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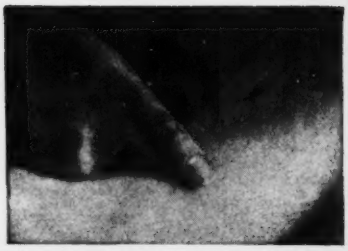

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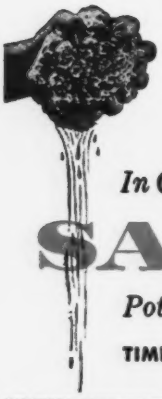

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Editorial

Pathogenesis of Essential Hypertension

THE pathogenesis of essential hypertension, which accounts for 95 per cent of hypertensions seen clinically, is still unknown despite extensive research during the past 25 years. These studies, however, have indicated that there are neurogenic, electrolyte, endocrine, and renal changes in pathophysiology that may have pathogenetic significance for essential hypertension. These changes may be interpreted to mean either that essential hypertension is a generic classification consisting of several distinct types of hypertension or that it is a single clinical entity with various degrees of functional alteration in different body systems. The former is presently the majority opinion, although only future research can determine which viewpoint is valid.

The pathogenetic relation of malignant hypertension to essential hypertension is also controversial. Although some authorities regard the 2 conditions as qualitatively different, most probably malignant hypertension is usually a greatly accelerated and accentuated form of essential hypertension. The same may be said for arteriolonecrosis, the typical lesion of malignant hypertension, in relation to arteriolosclerosis, the typical lesion of essential hypertension.

Recent reports confirm the role of heredity and body type in essential hypertension, but obviously these factors must operate through pathogenetic and pathophysiologic mechanisms that only future research can elucidate. Aging and obesity are contributory but not basic factors in the development of essential hypertension. The cardiac output, blood volume, viscosity of the blood, and elasticity of the arteries are within normal limits in early essential hypertension. The hypertension is due to increased resistance offered by the systemic arterioles, which in the beginning is due to increased tonus of arteriolar smooth muscle. Basically then, elucidation of the pathogenesis of essential hypertension involves determination of the mechanism responsible for increased tonus of arteriolar smooth muscle.

The neurogenic factor in essential hypertension is considered by its proponents to have origin in nervous tension or corticohypothalamic imbalance, as a consequence of which the vasomotor system is periodically and later continuously set at a higher level of activity with resultant increased tonus of the smooth muscle of the systemic arterioles. The evidence for this concept is circumstantial and includes the antihypertensive effects of tranquilizing, sedative, and vasomotor blocking drugs in some patients and the apparent curative effect of sympathectomy in 5 to 10 per cent of patients. One recent report denies increased vasomotor nerve activity in essential hypertension,[1] and certainly the burden of proof rests on those who maintain that such activity is chronically operative and pathogenetic in essential hypertension.

There have been many attempts to produce persistent hypertension by alteration of the nervous system of animals. Some of these have been successful. Strong auditory stimulation of rats selected for emotional instability leads to hypertension that has not been sufficiently studied to determine its pathophysiology. Section of the buffer regulatory (carotid sinus and aortic depressor) nerves produces a high-level hypertension in dogs and rabbits. While buffer-nerve hypertension differs in important

respects from essential hypertension; viz., increased cardiac output, increased heart rate, chronically increased vasomotor tonus, and absent buffer-nerve reflexes, its further investigation may yet yield information of value for a better understanding of essential hypertension. A persistent, low-level hypertension has been produced in a few dogs by successive ligation in the neck of the arteries supplying the brain. Recently a mild hypertension has been produced in rabbits by ligation of the internal and external carotid arteries.[2] A high-level, persistent hypertension has been produced in dogs by constriction of the branches of the carotid arteries above the carotid sinus.[3, 4] Since the hypertension of these dogs appears to resemble essential hypertension, its further study may be important to our knowledge of essential hypertension.

The possibility that essential hypertension may be due to increased secretion of an as yet unidentified adrenal cortical steroid with a pronounced pressor effect and minimal effects on sodium and carbohydrate metabolisms is suggested by the demonstration of mild alterations in sodium and water metabolisms in essential hypertension. Thus the patient with essential hypertension retains sodium and water more readily than the normotensive person on a sodium-free diet, loses more sodium in the urine under hydropenic conditions, excretes more sodium and water under load, and shows an increased sodium content of the renal arteries and psoas muscles. Moreover, a minority of patients with essential hypertension shows a significant reduction in blood pressure on a low-sodium diet. Whether these changes in sodium metabolism are cause or effect in relation to the pathogenesis of essential hypertension remains to be determined.

There is a recent report of increased aldosterone in the urine in essential hypertension.[5] Also mild adrenal cortical insufficiency resulting from adrenalectomy and minimal substitutive therapy produces an antihypertensive effect in some patients with severe essential and malignant hypertension. A minority of patients with essential hypertension shows increased norepinephrine in the urine[6] and according to a recent report, patients with essential hypertension show increased antidiuretic hormone in the urine.[7] Certainly a more thorough study of the anterior pituitary, adrenal cortex, and other endocrines in essential hypertension is needed, particularly with the improved methods for determining adrenal cortical steroids now available. Presently the burden of proof is on those, including Selye, who maintain that altered anterior pituitary-adrenal cortex function is pathogenetic in essential hypertension.

Large doses of crude anterior pituitary extract, somatotrophic hormone, desoxycorticosterone, aldosterone, or sodium chloride produce hypertension in rats, but less readily or not at all in dogs. Although these experimental hypertensions appear to resemble those of patients with pituitary basophilism or adrenal cortical tumors rather than essential hypertension, their further study may throw light on the pathogenesis of essential hypertension.

From the time of Bright, clinical hypertension was regarded as usually of renal origin, but at the end of the last century the concept rose that essential hypertension is of unknown cause and not due to renal mechanisms. This concept still dominates clinical thinking, although challenged by Goldblatt and other laboratory workers. The absence of commonly measurable changes in renal function in early essential hypertension does not rule out the possibility of more subtle changes in renal physiology that may be pathogenetic. The possibility of such changes is suggested by the presence in essential hypertension of an increased plasma concentration of vasoexcitatory material (VEM) produced by the kidney, an altered tetrazolium histochemical pattern in the kidney, and the ability of the kidney to form VEM aerobically. In contrast to normotension, these findings are also present in experimental renal hypertension that is produced by constriction of the renal arteries in dogs.

Failure to find a difference between the renin concentration of the plasma in normotension and essential hypertension has frequently been cited against a pathogenetic role for renin and the kidney in essential hypertension. However, recently it was shown that hypertension could be maintained by the intravenous infusion of rabbit renin into the rabbit in an amount that

produced an increase in plasma renin concentration not detectable by present methods of assay.[8] Moreover, by means of a technic employing 250 ml. of blood per determination, the hypertensin content of the blood has been reported increased in essential hypertension.[9] This finding suggests that the renin content of the plasma in essential hypertension should be reassayed with the use of larger amounts of blood. Obviously the burden of proof is still on those who believe that the kidney is pathogenetic in essential hypertension. In any event, renal arteriolosclerosis developing during the course of essential hypertension can accentuate and accelerate the course of the hypertension on the basis of Goldblatt's classic experiment.

Constriction of the renal arteries, a figure-of-eight tie or a cellophane capsule about the kidneys, or injection of a silica solution into the renal arteries produces hypertension in various species of laboratory animals that resembles in many respects essential hypertension. Severe constriction of the renal arteries produces experimental malignant hypertension. Obviously the similarities of these experimental hypertensions to essential and malignant hypertensions in man do not necessarily mean even a partially common pathogenesis. Complete nephrectomy with renal excretory function substituted by peritoneal lavage or the artificial kidney, produces hypertension in dogs and rats, but its relationships to experimental renal hypertension and essential and malignant hypertension are still obscure. Nevertheless, continued study of these experimental hypertensions is important for our understanding of essential hypertension.

Antirenin to hog renin that is actively produced or passively administered is antihypertensive in dogs with experimental renal hypertension,[10] renal (pyelonephritic) hypertension, and spontaneous (essential?) hypertension,[11] suggesting that these hypertensions are on a renal, renin basis. Unfortunately, while antirenin to hog renin neutralizes dog renin, it does not neutralize human renin. A number of attempts to modify the antigenicity of hog renin so that its antirenin will neutralize human renin have been unsuccessful.[12] If a future attempt should succeed, the way would be clear to determine what percentage, if any, of patients with essential hypertension have their hypertension on a renal, renin basis. Antirenin to human renin that is prepared in the dog, which neutralizes only primate renins, is antihypertensive on passive administration to monkeys with hypertension produced by renal artery constriction.[13] We are presently stockpiling antirenin to human renin with a view to a similar experiment in essential hypertension. Although human and monkey renins are similar antigenically, human renin produces an antirenin in the monkey that exerts an antihypertensive effect in experimental renal hypertension in this species.[13] The possibility of the reverse experiment in essential hypertension is hampered by the minute amount of renin in monkey kidneys, but the number of kidneys used per year for poliomyelitis virus culture would be sufficient for a crucial experiment.

Since the pathogenesis of essential hypertension is unknown, treatment must be based on pathophysiology and empiricism. Current treatment affords symptomatic relief and prolongs life in some patients but whether it is capable of altering the basic cardiovascular disease process can only be conjectured. To the degree that present therapy exerts an antihypertensive effect, it should delay the onset and progress of arteriolosclerosis and atherosclerosis.

Obviously much work remains to be done. Neurogenic, endocrine, and renal factors in essential hypertension must be further explored and other avenues investigated. The possibility of a basic pathogenetic change in the contractile proteins, electrolytes, enzyme systems, and other metabolic processes of vascular smooth muscle must be studied. The normality of pulmonary arterial pressure in early essential hypertension has been too readily explained on the basis of the sparse smooth muscle of the pulmonary arterioles. Long-term physiologic, psychologic, sociologic, and epidemiologic studies may yield important information. Barring a fortunate, accidental finding, treatment will be specific, curative, and preventive only when the pathogenesis of essential hypertension is determined.

GEORGE E. WAKERLIN

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Mönckeberg's Arteriosclerosis. Dr. J. G. Mönckeberg (1878–1925) first wrote of "Calcification Confined to the Media of the Arteries of the Extremities and its Relation to Arteriosclerosis" (*Über die reine Mediaverkalkung der Extremitätenarterien und ihr Verhalten zur Arteriosklerose*) in Virchow's *Archiv für pathologische Anatomie und Physiologie und für klinische Medicin* 171: 141–167 (January 2), 1903, when he was working in the pathological-anatomical institute of the General Hospital at Hamburg-Eppendorf.

"In conclusion I should like to state:

"1. Calcification of the media is much more frequent in the arteries of the extremities than arteriosclerosis.

"2. If the arteries of the extremities are palpable as 'stiff, tortuous, brittle tubes,' we are dealing in an overwhelming majority of the cases with a calcification of the media, not with arteriosclerosis.

"3. It is not possible to decide without other evidence as to the existence of arteriosclerosis of the central vessels, either from the degree or the extent of peripheral calcification of the media. Both diseases are frequently found together, but cases occur of very marked medial calcification of the peripheral arteries without any arteriosclerosis of the internal vessels."

Present Status of Diagnosis and Treatment of Pheochromocytoma

By U. S. von Euler and G. Ström

For detection and diagnosis of pheochromocytoma the method of urine analysis is considered the most convenient, safe, and accurate. Analysis of blood samples obtained by catheterization at different levels in the vena cava aids in localization. Some features of the clinical symptomatology and the pharmacologic and operative treatment of patients with chromaffin-cell tumors are given.

PHEOCHROMOCYTOMA is a neoplasm of the chromaffin cells of the sympathetic nervous system (adrenal medulla, aberrant tissue near the sympathetic chain, paraganglia). Its occurrence in man is known from early reports of autopsies.[1] It is now being diagnosed in vivo with increasing frequency, partly because the characteristic clinical syndrome[2] that is produced by the secretion of chromaffin cell hormones from the tumor (norepinephrine and epinephrine) has been duly recognized, and partly because valid and relatively precise methods for the laboratory diagnosis have been developed.

The tumor usually develops in adult life, slightly more often in women than in men, but may occur in children;[3] it is usually situated in or near the adrenal glands but may be found at other places along the sympathetic chain;[4, 5] it may be multiple and may also be malignant in a minority of cases;[6, 7] it may show familial occurrence[8, 9] and is sometimes associated with neurofibromatosis.[10, 11]

The untreated tumor usually leads to a fatal outcome within a relatively short number of years with a clinical course resembling that of malignant hypertension. An increasing number of cases is being reported where surgical complete removal of the tumor[12] has led to partial or complete reversal of the structural and functional changes in the circulatory system that had developed before operation.

Symptomatology

A pheochromocytoma may give local symptoms due to its increasing size; these are not considered here. The tumor with rare exceptions retains the secreting function of the chromaffin-cell system, as evidenced by an augmented urinary excretion of norepinephrine and sometimes also of epinephrine. Malignant metastases may also be actively secreting.[13] The exaggerated secretion of catechol amines into the circulation leads to systemic changes[14] that can be predicted from the present knowledge of the physiologic effects of norepinephrine and epinephrine (table 1).

In accordance with expectations, an actively secreting pheochromocytoma produces several or all of the following main changes: arterial hypertension with increase of systolic as well as diastolic blood pressure; no consistent change of resting pulse rate; increased sweating; cutaneous vasoconstriction; increase of basal metabolism; increase of fasting blood sugar concentration and sometimes glucosuria; central nervous excitation.[2, 15-17] In some cases the augmented secretion of catechol amines occurs intermittently with "paroxysms" of effector reactions, but in the majority of patients it is continuous. The subjective experience of the patient is usually dominated by headache, sweating, nervousness, and loss of weight. When these symptoms occur in paroxysmal attacks the case history may be immediately suggestive of pheochromocytoma but it is more difficult to evaluate when the symptoms are continuously present. In the latter case, the usual sequence of vascular changes in the retinal, coronary, cerebral, and renal areas secondary to prolonged arterial hypertension will appear. At this stage the clinical picture may simulate essential hypertension.[18] Although pharmacologic tests (provocative or blocking) may still be helpful in establishing the correct diagnosis, this ultimately has to rely on the estimation of the urinary excretion (or blood concentration) of

TABLE 1.—*Effects of Circulating Norepinephrine (NE) and Epinephrine (E)*

Effector system	Response to	
	NE	E
Isolated heart	Positive inotropic and chronotropic	Positive inotropic and chronotropic
Heart frequency in vivo	Bradycardia	Tachycardia
Mean arterial blood pressure	Increase	Slight increase or decrease
Skeletal muscle	Vasoconstriction	Vasodilatation
Liver	Vasoconstriction	Vasodilatation
Skin	Vasoconstriction	Vasoconstriction
Kidneys	Vasoconstriction	Vasoconstriction
Sweat glands	Activation	Activation
Intestinal smooth muscle	Relaxation	Relaxation
Pupils	Weak dilatation	Dilatation
Central nervous system	No effect	Apprehension, excitation
Blood sugar	Slight increase	Increase
Basal metabolic rate	Slight increase	Increase
Blood eosinophils	Slight fall	Fall

catechol amines.[19] The electrocardiographic changes that often appear do not seem to be specific.[20]

PHYSIOLOGIC DIAGNOSTIC METHODS

Urinary Excretion of Catechol Amines. Holtz and associates[21] gave the first evidence that the adrenal medulla of the cat produces norepinephrine as well as epinephrine. The occurrence of norepinephrine in chromaffin-cell tumors was demonstrated by Holton[22] and soon confirmed by several workers. In 1950 Engel and Euler[23] showed that large amounts of norepinephrine were secreted in the urine in 2 cases of hypertension in which subsequently pheochromocytomas were found and removed. In 1 of these cases also epinephrine was secreted in large amounts in the urine. The diagnostic value of this finding was pointed out and the method of urine analysis has since been used extensively for the diagnosis of pheochromocytoma. This method has several advantages over other methods used for the diagnosis. It incurs no risk or inconvenience to the patient and can be repeated frequently. Since the method is based on quantitative estimation of the pathogenic factor, there is hardly any risk of false positive or false negative results, which not infrequently occur with other methods. Moreover, the test gives quantitative information on the activity of the tumor, which is not obtained with other tests.

TABLE 2.—*Daily Urinary Excretion of Norepinephrine and Epinephrine in Case no. 21 (operated on Oct. 1, 1954)*

Date	Diuresis ml./24 hr.	Urinary norepinephrine excretion μg./24 hr.	Urinary epinephrine excretion μg./24 hr.
June 28 1954	2.100	418	10
July 7	1.400	630	12
Sept. 16	1.700	990	not analyzed
18	1.040	1.040	not analyzed
20	950	810	not analyzed
22	1.300	1.560	not analyzed
23	1.600	1.600	not analyzed
24	2.000	1.400	not analyzed
Oct. 2	1.500	162	21
3	700	81	11
4	1.500	68	8
5	1.150	68	7.9
Nov. 10	1.350	70	1.3
17	1.070	52	2.2
Dec. 16	1.900	37	9.2
17	1.590	47	2.6
Oct. 6 1955	1.950	96	2.8
7	1.000	30	0.12
8	2.000	120	1.2
Feb. 3 1956	1.110	110	1.1
22	1.300	117	0.77
Apr. 19	1.300	140	3.6
May 16	1.745	63	0
June 15	1.310	123	1.6

Several technics for the estimation of the urinary catechol amines have been described.[24-27] A relatively simple method suitable for routine determinations in clinical laboratories has recently been elaborated by Euler and Floding.[28] This technic is based on the adsorption of the catechol amines on aluminium oxide, elution with acid, and fluorimetric estimation of the stabilized fluorescent products obtained by oxidation with ferricyanide at different pH.

The urinary output of catechol amines in cases of pheochromocytoma varies according to the conditions, but in the presence of an actively secreting tumor it is invariably increased. This increase is based on the fact that circulating catechol amines are excreted in the urine in a fairly constant proportion[29-33] of approximately 1 to 5 per cent of the adminis-

tered amount. When urine from a case with tumor is collected over a period of 24 hours, variations in the output during the day will be smoothed out and a representative figure is obtained. This is evidenced by the relative constancy of the output during a series of subsequent days[34] (table 2). A continuous release of catechol amines from the tumor is also borne out by the production of a permanently high blood pressure level. Even in cases characterized by paroxysmal attacks and with approximately normal blood pressure between the attacks, the 24-hour catechol-amine values were found elevated in our cases. Removal of the tumor is usually followed by a return of blood pressure to normal levels and a precipitous fall in the catechol-amine excretion. The urinary output of norepinephrine is sometimes slightly elevated even after the operation; this persistence may be due to a compensatory increase in vasomotor activity. Normal figures are usually found after a lapse of 1 to 2 weeks.

Table 3 gives the available data from 35 cases of pheochromocytoma that have been subjected to urine analysis in our laboratory and in which the location and nature of the tumor have been verified at operation and in most cases also by microscopic examination.

The results may be summarized as follows: 1. In all cases showing clinical signs of a secreting tumor the catechol-amine excretion in the urine is increased. 2. There is good agreement between the proportion of norepinephrine and epinephrine in the tumor and in urine. 3. While norepinephrine is increased in the urine in all cases of secreting tumors, epinephrine is increased only in certain cases. 4. In no instance of pheochromocytoma was increased content of epinephrine alone found in the urine or in the tumor.

Since norepinephrine is normally excreted in urine in amounts of about 20 to 40 μg./24 hours and may be considerably increased in various clinical conditions (trauma, surgical stress, fever, burns, myocardial infarction), there is no exact way of deciding the lower limit of excretion that indicates a tumor. The lowest 24-hour values of urinary catechol amines accompanying verified tumors have been 104 and 109 μg. (case 10 and 17 in table 3). In 32 of our 35 cases the urinary excretion exceeded 300 μg./24 hours. For practical purposes a daily excretion of 100 to 200 μg. of norepinephrine may be regarded as the lower limit for the diagnosis of a clinically active tumor. It is also of value to establish such a limit, since lower excretions may be due to tumors that are not big enough to allow surgical detection.

Blood Content of Catechol Amines. While the urine analyses permit integration of the tumor secretion over an arbitrary length of time, the blood estimations give information about the catechol-amine concentration at any given moment. This may be of value for instance during an attack, and may allow a differentiation of pheochromocytoma from vasomotor crises, which should show lower blood catechol-amine levels for a given rise in blood pressure than a secreting tumor.

Using the method of fluorimetric estimation, Lund[24] was able to show unequivocally that the blood catechol-amine levels were greatly increased in several cases of chromaffin-cell tumors, the values varying between 14 and 98 μg./L. as against less than 1 μg./L. in normal peripheral venous blood (table 4).

Adrenal Cortical Activity in Cases of Pheochromocytoma

The eosinopenic action of epinephrine was earlier taken as evidence for a release of cortical hormones. Direct estimation of corticoid hormones have failed, however, to show any increase after infusion of epinephrine.[35]

Normal or low 17-ketosteroid figures in urine have been reported by several authors.[36, 37] Normal 17-OH-CS values in the blood were found in a case of norepinephrine-producing pheochromocytoma,[34] while an increased 17-OH-CS level, 17 μg./100 ml., was observed by Querido[38] in a case of a tumor that released epinephrine as well as norepinephrine.

Eosinopenia has been noted in certain cases of pheochromocytoma but neither the white cell count nor the corticosteroid level in blood or excretion in urine seem to be of any specific diagnostic value in pheochromocytoma.

TABLE 3. *Thirty-five Cases of Pheochromocytoma with Urine Analysis of Catechol Amines, in Most Cases Verified at Operation and by Microscopic Examination.*

Case No.	Age	Sex	Hypertension	Localization	Urinary NE μg./24 hr.	Urinary E μg./24 hr	Tumor NE mg./Gm.	Tumor E mg./Gm.	Tumor size (Gm.)
1	43	F	—	in right adrenal	125–153	59–103	2.1	1.5	525 (cyst)
2	33	F	perm.	close to adrenal	234–875	28–138	1.3	0.15	ca 4
3	49	F	perm.	close to aorta at umbilical level	437–1240	11–54	4.6	0.1	45
4	44	F	perm.	in right adrenal	113–660	110–780	0.75	0.75	20
5	42	F	parox.	at site of right adrenal	345–384	164–224	7.4	2.3	147
7	25	F	perm.	between aorta and duodenum	1790–2250	18–24	8.4	0.1	50
8	26	M	—	in left adrenal	240	68	—	—	—
10	50	M	perm. + parox.	in right adrenal	104	not determined	—	—	28
11	23	M	perm.	adherent to left adrenal	1010–1200	16–19	0.63	0.07	40
12*	30	F	perm.	between abdominal aorta and vertebral column	415	11	—	—	—
13	40	F	perm.	in left adrenal	240–327	8.4–26	5.2	0.1	ca 4
15†	56	F	perm.	refused operation	1290	38	—	—	—
16	61	M	—	at site of right adrenal	918	540	—	—	500
17	—	M	—	close to right adrenal	23–83	49–126	0.001	0.003	28 (fluid not included)
18	6	M	perm.	adherent to left adrenal	3000	5	4.0	0.1	19
19	44	M	perm.	at site of left adrenal	450, 640	430, 540	0.63	1.3	270
20	13	M	perm. + parox.	close to right adrenal	1450	7.5	—	—	ca 50
21	26	F	perm.	at left renal hilus	418–1600	10–12	3.8	0.1	17
22	26	F	perm.	at aortic origin of inf. mesent. art.	750, 800	3.1	1.1	0.1	37
23	47	M	perm. + parox.	close to left adrenal	450	2.9	—	—	walnut
24†	—	M	perm.	suspected general spread	8800	low, not demonstrable	—	—	—
26	34	F	perm.	in right adrenal	213–618	2.1–15	1.5	0.1	20
27	41	M	parox.	at site of left adrenal	496	538	—	—	ca 50
29	29	M	perm. + parox.	at site of left adrenal	1040, 1160	4.5, 14	2.8	0.25	85
30	31	M	perm.	multiple tumors in thorax	1400–1800	1.5–9	0.2	0	ca 76
31	46	M	perm.	tumor not found at operation	390	19	—	—	900 (cyst)
32	40	F	perm. + parox.	close to right adrenal	1360, 1400	3, 4, 6.5	—	—	—
33	59	F	perm.	two tumors between adrenal and kidney	162, 300	170, 310	—	—	small egg large egg
34‡	35	M	perm.	between aorta and vertebral column at duodenal level	520	33	—	—	fist
35	51	M	parox.	in right adrenal	280	294	—	—	plum
36	45	M	perm.	between aorta and duodenum	2100	4.3	—	—	440
37	6	F	perm.	in right adrenal	2060	7.4	3.3	0	11
38	49	F	perm.	close to right adrenal	352	23	—	—	—
39	45	M	perm.	in right adrenal	398	9.3	—	—	—
40	37	F	perm.	at site of left adrenal	1420	280	—	—	fist

Perm. = permanent
Parox. = paroxysmal.

* Case 12: ganglioneuroma + pheochromocytoma

† Case 15 and 24: not operated.

‡ Case 34: adrenal cortical carcinoma, probably including pheochromocytoma.

TABLE 4.—*Epinephrine (E) and Norepinephrine (N) in Venous Blood from Patients with Pheochromocytoma (Lund 1952)*[24]

Case no.	During attack (blood pressure)	After attack (blood pressure)
2	a) 2.4 μg. % N + E (300 mm. Hg)	<0.3 μg. % N + E (150 mm. Hg)
	b) 2.1 μg. % N (300 mm. Hg)	<0.3 μg. % N + E (after operation)
4	9.8 μg. % N + E (260 mm. Hg)	<0.4 μg. % N + E (130 mm. Hg)
5	a) 3.4 μg. % N (+E)	—
	b) 3.8 μg. % N (+E)	
6	1.4 μg. % N + E (260 mm. Hg)	1.4 μg. % N + E (? mm. Hg)
7	4.4 μg. % N + E (235 mm. Hg)	—
Normal		<0.1 μg. % N + E

DRUG TESTS FOR PHEOCHROMOCYTOMA

A large number of papers have been published on the diagnostic use of various drug tests in pheochromocytoma. The basic principles for these tests have been either release of active amines from the tumor or depression of their actions. Although these tests may supply information as to the presence or absence of a chromaffin-cell tumor they not infrequently give false positive or false negative results, which restrict their clinical value. In many instances they cause inconvenience or incur risks to the patients, even with fatal results. As a general rule the attack-producing drugs should not be given unless the blood pressure is normal or only slightly elevated, whereas the antisympathomimetic drugs are only useful during increased blood pressure. Since simple clinical laboratory methods for the estimation of the catecholamine output in urine now are available, it would seem that the less reliable drug tests should be used in exceptional cases only, in conjunction with urine analysis, or as an emergency method when urine analysis is not available.

Some of the most widely used drug tests are, however, briefly reviewed.

1. *Histamine Test* (Roth and Kvale[39]). This test is based on the direct stimulating effect of histamine on the chromaffin cells, causing a release of catechol amines and rise in blood pressure. After intravenous injection of 25 to 50 to 100 μg. of histamine (in terms of the base) a large rise of blood pressure is usually recorded in cases of pheochromocytoma while the rise in other cases is as a rule either absent or relatively small.

2. *Mecholyl Test* (Guarneri and Evans[40]). This test like the foregoing one depends on direct stimulation of the chromaffin cells. The doses used are 10 to 25 mg. subcutaneously. Both the histamine and the mecholyl tests are relatively nonspecific and may give misleading results. In addition, these tests may cause inconvenience and even certain risks for the patients by raising the blood pressure to very high levels in tumor cases and by producing a fall of blood pressure in other cases. Before the injection of Mecholyl the patient should be given 1 mg. of atropine sulfate. In this group also falls 1,1-dimethyl-4-phenyl piperazonium iodide (DMPP), a ganglionic-stimulating agent.[41]

3. *Benzodioxane Test.* This was introduced by Goldenberg and associates.[42] The injection of 0.25 to 0.50 to 0.75 mg./Kg. body weight causes a prompt drop in blood pressure, which returns to the pre-injection pressure in a few minutes or up to about 1 hour later. A usual test dose is 15 to 20 mg. of benzodioxane hydrochloride intravenously.

Although this test is said to be more specific than the foregoing ones, it is not entirely innocuous. Thus strong and rapid pressor responses (over 300/200 mm. Hg) have been observed.[43]

4. *Dibenamine Test.* Slow intravenous injection (over 1 to 2 hours) of 400 mg. of dibenamine hydrochloride in 500 ml. of 5 per cent glucose solution causes a slowly developing but long lasting (11 hours) lowering of the blood pressure in pheochromocytoma.[44] Dibenamine in a dose of 10 mg./Kg. body weight may also block the releasing effect of histamine.[45]

5. *Phentolamine (Regitine) Test.* This drug, which blocks the effector cells for the action of epinephrine and norepinephrine like Benzodioxane and Dibenamine, was introduced by Longino and co-workers.[46] It has been claimed to be the safest of the antisympathomimetic test drugs. When given in a dose of 5 to 10 mg. intravenously, it causes a fall in blood pressure often lasting for more than an hour in tumor cases. False positive reactions are not infrequent.[37, 47]

6. *Tetraethylammonium Test* (LaDue, Murison, and Pack[48]). This drug acts as a ganglionic-blocking agent and is thought to increase the pressor action of circulating norepinephrine and epinephrine by blocking the regulating mechanism. In addition it seems to cause an increased release of the chromaffin cells by direct action. It is seldom used.

Localization of Tumor

It is highly desirable that the exact localization of the tumor or tumors in the body is known before operation. In some cases the tumor is relatively large and therefore possible to palpate or to observe on a plain roentgenogram (10 to 30 per cent of cases[7, 49, 50]). Usually it is small (weight less than 100 Gm.) but palpation may nevertheless give information if the arterial blood pressure is found to increase significantly when the suspected site is palpated.[51, 52] Other examinations may give successful results, such as intravenous or retrograde pyelography (positive result in 20 to 50 per cent of cases[7, 50]), selective arteriography,[53] tomography, and retroperitoneal gas insufflation (positive result in about half the examined cases[7]).

Suggestive information may also be obtained from analyses of the catechol-amine concentration in urine and blood. As is evident from table 3, a pheochromocytoma releasing norepinephrine as well as epinephrine is usually localized in direct connection with 1 of the adrenal glands, while a tumor producing only norepinephrine is usually situated more or less away from the adrenal glands. There are exceptions to this rule, however.

A new approach has recently been tried.[34] By introduction of a radiopaque catheter (the usual cardiac catheter or better the special type used by Ödman[54]) under fluoroscopic control, blood samples can be drawn from selected parts of the venous system. Venous blood from the tumor may have a sufficiently high concentration of catechol amines to allow a relatively precise estimation. The catechol amines become diluted in the caval veins but if samples are obtained just central and distal to the level of entrance the result may be conclusive. If the catheter tip is introduced into the renal veins (and exceptionally into the right adrenal vein) the result may indicate that an adrenal tumor is right-sided or left-sided. In 1 case[34] (case no. 21 in table 3) an extra-adrenal tumor at the left renal hilus was observed at operation to be drained by a vein entering the inferior caval vein caudal to the level of the renal veins. The catheterization study had shown that norepinephrine was absent in the superior caval vein but present in increasing concentration when the catheter tip was moved down toward the iliac bifurcation of the inferior caval vein. In a second case of malignant pheochromocytoma[55] (case no. 24 in table 3) with suspected general spread of metastases, high norepinephrine concentrations were found in the inferior as well as the superior caval systems (but not in arterial blood). In a third case[56] (case no. 30 in table 3) of a multiple, possibly malignant, intrathoracic pheochromocytoma, samples from the inferior caval vein and the brachiocephalic veins did not contain norepinephrine, but a high concentration appeared in the superior vena cava at the level where the azygos vein usually enters. To judge from these 3 cases, selective venous catheterization with blood analysis of catechol amines may be of clear value for the topical diagnosis of continuously secreting pheochromocytomas. A similar procedure has been used for evaluation of unilateral adrenal cortical activity;[57] in the case of a unilateral adrenal pheochromocytoma it may be of value to examine the cortical function of the contralateral adrenal gland before operation.

Treatment

The adequate treatment of pheochromocytoma is the complete surgical removal of the tumor.[12, 58] This may be difficult, since the tumor often is situated near the aorta and the inferior vena cava, and since it may easily rupture even if it is encapsulated. The mortality rate of operations has hitherto been high (20 to 30 per cent)[59] but will probably become lower with more adequate postoperative treatment. Antisympathomimetic agents (Benzodioxane, Dibenamine, or preferably Regitine) can be used temporarily to combat a spontaneous paroxysmal attack, or an attack provoked by pharmacologic diagnostic stimulation, or diag-

nostic palpation, or by the anesthesia and the manipulation of the tumor during operation.

Difficulties may arise in keeping the arterial blood pressure within reasonable limits during operation. For the exact and rapid pharmacologic treatment of sudden changes in arterial pressure, it is of advantage to register the pressure continuously, e.g., with the technic for intra-arterial recording described by Holmgren.[60] The body position of the patient during operation[61] and the choice of anesthetics[16, 62, 63] may be of importance for the catechol-amine release from the tumor. When the tumor has been removed, intravenous administration of norepinephrine for a variable length of time and sometimes in high dosage[64] is usually necessary to prevent the arterial blood pressure from falling below the normal range.

The urinary output of catechol amines should be determined after operation in order to ascertain the completeness of the surgical treatment.[13, 65] A high arterial blood pressure after an apparently successful operation may be due to essential hypertension existing before the appearance of the tumor, or to vascular changes secondary to the period of elevated blood pressure caused by the tumor, or may be produced by remaining undetected tumor tissue. Urinary analysis of catechol amines may help to differentiate these possibilities.

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Storstein, O., and Tveten, H.: Quinidine Treatment of Established Auricular Fibrillation. Acta med. scandinav. **153:** 57 (Dec. 16), 1955.

All patients with established atrial fibrillation admitted to the Nordland County Hospital during a period of 18 months were treated with quinidine in an attempt to restore normal sinus rhythm. The patients were treated with digitalis and Dicumarol before and during the period of quinidine therapy. Of a total of 74 patients, normal sinus rhythm was achieved in 45 (60.8 per cent). It was found that the lowest percentage of conversions occurred in patients with rheumatic heart disease. The longer the duration of the atrial fibrillation the greater was the difficulty in achieving normal rhythm. When normal rhythm was produced, the circulation time was found to be shorter and the roentgenologic heart volume was found to decrease, but the venous pressure did not change appreciably. Nausea, vomiting, or diarrhea during treatment occurred in 19 per cent of the patients. Sixteen per cent of the patients showed quinidine effects upon the electrocardiogram including ventricular premature beats, widening of the QRS complexes, nodal rhythm, atrioventricular block, and nodal tachycardia, which required discontinuance of quinidine treatment. After the drug was stopped, one half of the patients developed sinus rhythm. Eight patients developed atrial flutter during the quinidine treatment. The authors believe that nothing is to be gained by increasing the quinidine dosage when this happens. However, by continuing the quinidine in a dosage of 0.3 Gm. 4 times daily and increasing the digitalis dosage to 0.1 Gm. 4 times daily, it was possible to produce sinus rhythm in 6 of these 8 patients. Of the 45 patients who were converted to normal rhythm, the conversion was maintained in 32 (71 per cent) during an observation period ranging from 3 to 24 months.

In connection with the conversion to sinus rhythm 2 patients developed emboli and 1 patient had a period of syncope that was attributed to cardiac standstill. Eleven of the patients had 1 or more emboli before treatment. It is thought that pretreatment with anticoagulants will reduce the danger of embolization. The toxic effects of quinidine on the heart necessitate close and constant supervision of the patients with daily electrocardiograms and even more frequent observations if disorders of rhythm occur. For this reason it is believed that quinidine therapy of the kind used in these patients can be carried out only in the hospital. Discontinuance of treatment is indicated if the QRS complex widens by more than 25 per cent.

ROSENBAUM

Effect of Cardiac Contraction on Coronary Blood Flow

By David C. Sabiston, Jr., M.D. and Donald E. Gregg, Ph.D., M.D.

In the experimental animal the basic and controversial problem was studied of the influence of cardiac contraction on coronary blood flow. Normally beating hearts were perfused at a constant pressure, and coronary inflow and outflow were determined. In order to assess the role of systole, prolonged periods of ventricular asystole and fibrillation were induced and observations were made of the changes in coronary flow. With the cessation of cardiac contraction blood flow in the coronary arteries and coronary sinus rose appreciably. The results of these studies support the concept that contraction of the heart muscle, by compression of the myocardial vascular bed, behaves as a throttling mechanism and impedes coronary flow. The method employed permits a separation and quantitation of the effects on coronary flow resulting from cardiac contraction and the vasomotor state of the coronary vessels.

THE effect of organized cardiac contraction on flow through the capillary bed of the myocardium remains unsettled despite much work that has been done to elucidate this basic problem. Evidence has accumulated in support of 2 opposing viewpoints. One concept is that the shortening of the muscle fibers during systole compresses the vascular bed in the myocardium and acts as a "throttling" mechanism. The opposing view is that cardiac contraction "massages" or "kneads" the blood through the vascular bed and increases coronary flow. The primary objective in this study has been an evaluation of the effect of organized myocardial contraction on coronary flow in the intact animal. This problem has been attacked by the elimination of this factor by the induction of ventricular asystole or ventricular fibrillation. Comparisons have been made of coronary flow in the beating heart perfused at a constant pressure with those in the nonbeating heart under the same conditions.

Methods

Twenty-seven adult mongrel dogs were anesthetized with intravenous pentobarbital (25 mg./Kg.). Respiration was maintained through an endotracheal tube connected to a demand-valve apparatus supplied with oxygen. The left chest was entered through the fourth intercostal space and the pericardium was opened. The appropriate coronary vessels were than cannulated. The left coronary artery was dissected at its origin from the aorta and a specially designed brass cannula was inserted into it via the left subclavian artery and tied securely in place by means of a ligature. For study of the right, circumflex, or descending branches of the coronary arteries, the vessel was dissected and ligated close to its origin. A small glass or polyethylene cannula was inserted into the distal end for perfusion. For flow measurement in the coronary sinus a flexible polyvinyl catheter was introduced through the right atrial appendage into the sinus and maintained in place at its orifice by a suture ligature. A rotameter was placed in the circuit, and blood was returned to the superior vena cava via the external jugular vein. In some experiments blood was allowed to drain from the coronary sinus catheter to the atmosphere. Mean coronary arterial pressure was determined by use of a Statham strain gage.* A diagrammatic illustration of the experimental preparation is shown in figure 1.

Blood entering the coronary artery was first passed through a recording rotameter[1] connected to a carotid artery and between experimental observations this vessel supplied the coronary perfusion. For a short time prior to induction of asystole and during this period, blood was perfused from a reservoir at or near the prevailing mean aortic pressure. Heparin was used as an anticoagulant (200 mg. initially and 100 mg. each 30 min.). In some instances this was supplemented by pontamine-fast pink (150 mg./Kg. initially and each hour thereafter) or Treburon (35 mg./Kg. and 125 mg. each hour thereafter). Asystole was produced by direct stimulation of both vagus nerves in the neck with an Electrodyne stimulator† delivering 250 volts at a

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* Manufactured by Statham Instruments, Inc., Hato Rey, Puerto Rico.

† Manufactured by Electrodyne Co., Endicott St., Norwood, Mass.

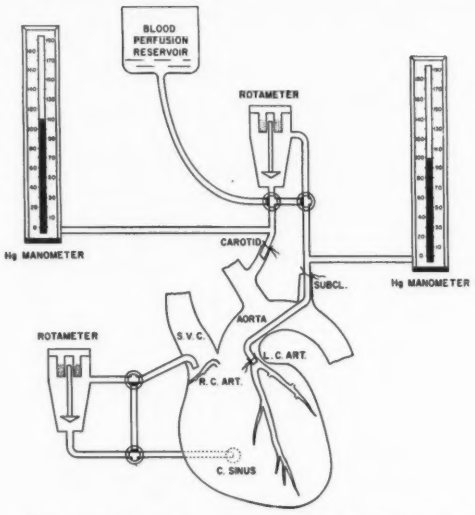

FIG. 1. Diagrammatic illustration of experimental preparation. A metal cannula was inserted in the left coronary artery and a polyvinyl catheter was sutured into the coronary sinus. Both were connected to rotameters for continuous recording of arterial inflow and venous outflow. The left coronary artery was perfused from the blood reservoir at a constant pressure.

frequency of 30/sec. This stimulus resulted in a period of asystole of 4 to 26 sec. Ventricular fibrillation was induced by direct stimulation of the left ventricle with an inductorium. A continuous recording of aortic and coronary perfusion pressure and coronary arterial and venous flow was obtained with an oscillograph.

RESULTS

A total of 248 observations of coronary flow with the heart in either asystole or ventricular fibrillation was made as follows:

Left Coronary Artery Inflow in Ventricular Asystole. There were 4 animals in which flow through the left coronary artery was studied and 40 inductions of prolonged asystole were performed. In each instance there was a rise in coronary flow after the onset of asystole. The average control flow was 93 ml./min. and following asystole it rose to 141 ml./min., representing an increase of 59 per cent (table 1). Maximal flow was reached in 1 to 4 sec. and remained elevated, although there was usually a slight fall with time. (In 2 later experiments in an unrelated study, coronary flow rose with asystole but fell later to a value below that of the control. Such a response was thought to be abnormal and probably the result of partial obstruction of the coronary sinus.)

TABLE 1.— *Flow in Left Coronary Artery and in Left Circumflex Coronary Artery in Ventricular Asystole*

Dog no.	Number of determinations	Average control flow ml./min.	Average flow during asystole ml./min.	Per cent increase in flow
Left coronary artery				
1	11	149	218	46
2	10	82	113	38
3	15	45	95	111
4	4	97	139	43
Average.....		93	141	59
Left circumflex coronary artery				
1	12	27	35	30
2	12	51	66	29
3	9	30	41	37
4	17	36	59	64
5	14	39	64	64
6	24	37	63	70
7	11	21	43	105
8	7	56	77	38
9	9	50	68	36
10	20	53	75	42
11	16	57	84	47
12	9	59	81	37
13	11	27	41	52
Average.....		42	61	50

Flow in a Left Coronary Artery Branch and in the Right Coronary Artery During Ventricular Asystole. The possibility was investigated of a difference in response of the coronary bed supplied by the right coronary artery or a major branch of the left coronary artery from that of the main left coronary artery. Two experiments were done with cannulation of both the right and left coronary arteries. Typical results during 1 of these experiments is shown in figure 2. Both right and left coronary arterial flows rose simultaneously, indicating that the beds supplied by these vessels respond in a similar manner during asystole.

A total of 171 determinations in 13 animals were made of coronary flow in the circumflex branch of the left coronary artery during ventricular asystole. In every instance flow rose

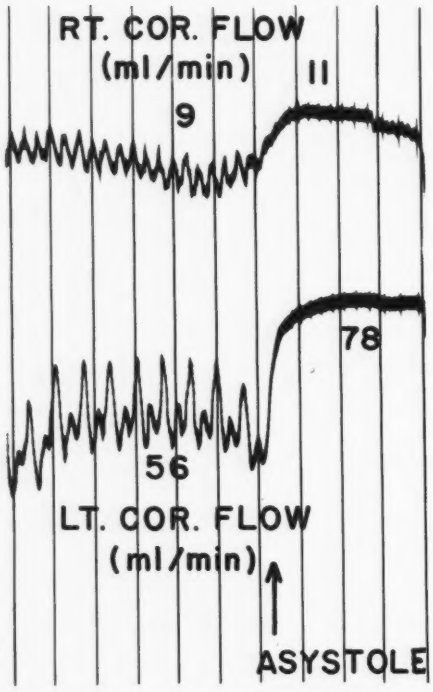

FIG. 2. Record illustrating flows in both right and left coronary artery. With the induction of asystole, flow increased in the left coronary artery from 56 to 78 ml./min. and in the right coronary artery from 9 to 11 ml./min. The time lines are 1 sec. apart.

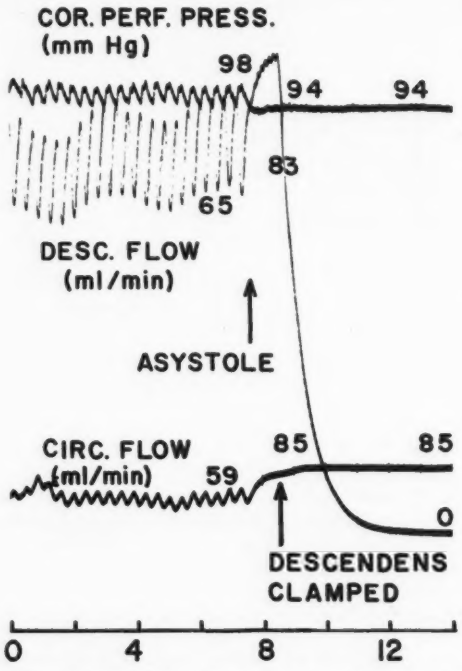

FIG. 3. Record showing control flows in circumflex (59 ml./min.) and descendens (65 ml./min.) arteries with a perfusion pressure of 98 mm. Hg. With induction of asystole flow in both vessels rose to 85 and 98 ml./min. respectively. When the descendens was occluded, circumflex flow remained constant. The record shows 7 seconds of asystole. Abscissa, time in seconds.

in the vessel as it was perfused at the preasystolic mean aortic pressure level. The average flow before asystole was 42 ml./min. and following asystole the value rose to 61 ml./min., representing an increase of 50 per cent (table 1). A typical record of the rise in circumflex flow during asystole is shown in figure 3.

Left Coronary Artery Inflow and Coronary Sinus Drainage in Asystole. In 3 animals, 6 determinations of both the left coronary arterial inflow and coronary sinus drainage were recorded during asystole while coronary perfusion was maintained at a constant pressure. Coronary arterial flow was always increased during asystole (31 to 77 per cent), with an average increase of 50 per cent. In each instance except 1, coronary sinus flow was also increased (table 2). Typically, there was an initial fall in coronary sinus drainage for 2 to 3 sec. and then it rose to exceed control values (fig. 4).

Coronary Arterial Inflow and Coronary Sinus Drainage in Ventricular Fibrillation. In 5 animals, a total of 8 simultaneous determinations of flow through the left coronary artery and the coronary sinus was made before and after the onset of ventricular fibrillation (table 3). The coronary inflow rose from 11 to 72 per cent, with an average increase of 26 per cent. The rise of flow in the coronary sinus varied from 16 to 76 per cent, with an average of 37 per cent. A typical record illustrating the increase in both arterial inflow and venous drainage is shown in figure 5. A rise in arterial flow in both the circumflex and descendens branches of the left coronary artery is also shown to occur with ventricular fibrillation.

The possibility must be considered that a portion of the augmentation of coronary inflow

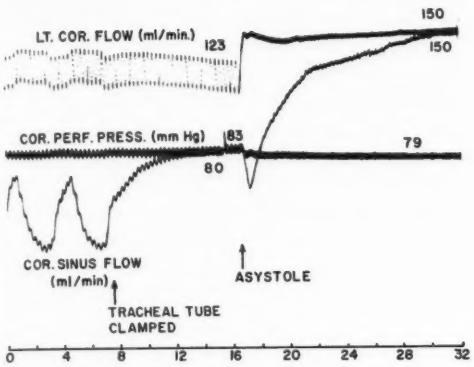

FIG. 4. Record illustrating control flow in left coronary artery (123 ml./min.) and in coronary sinus (80 ml./min.) with a perfusion pressure of 83 mm. Hg. During asystole both flows rose (coronary artery to 150 and coronary sinus to 150 ml./min.) at a perfusion pressure of 79 mm. Hg. The endotracheal tube was clamped prior to asystole to eliminate respiratory variations in coronary sinus flow. Abscissa, time in seconds.

TABLE 2.—*Left Coronary Artery and Coronary Sinus Flow in Ventricular Asystole*

No.	Left circumflex flow			Coronary sinus flow		
	Control (ml./min.)	In asystole (ml./min.)	Per cent increase	Control (ml./min.)	In asystole (ml./min.)	Per cent increase
1	119	156	31	72	86	19
	111	151	36	68	80	18
2	94	166	77	38	59	55
	105	168	60	62	52	−16
	95	142	49	34	48	41
3	142	209	47	94	108	15
Average.....			50			30

TABLE 3.—*Left Coronary Artery and Coronary Sinus Drainage in Ventricular Fibrillation*

No.	Left coronary artery flow			Coronary sinus flow		
	Control (ml./min.)	V. Fib. (ml./min.)	Per cent increase	Control (ml./min.)	V. Fib. (ml./min.)	Per cent increase
1	89	126	42	56	74	32
	103	119	16	68	88	30
2	123	145	18	38	45	18
	132	147	11	40	51	28
3	119	139	17	74	119	61
	124	146	18	86	151	76
4	134	159	19	82	114	39
5	81	139	72	43	50	16
Average.....			26			37

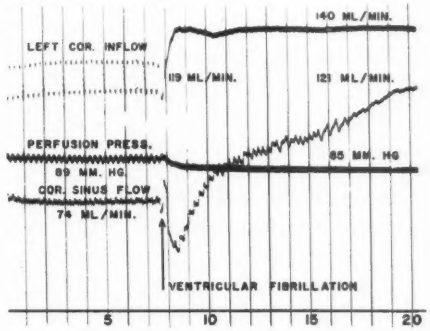

FIG. 5. Record illustrating flow changes in the left coronary artery and coronary sinus during ventricular fibrillation. Flow rose in the left coronary artery from 119 to 140 ml./min. and in the coronary sinus from 74 to 121 ml./min. Perfusion pressure remained essentially constant at 85 to 89 mm. Hg. Time lines are 1 sec. apart and are numbered on abscissa.

with removal of coordinated ventricular contraction is related to events other than prolongation of the period of diastole. During asystole the central pressure and flow in a coronary artery or branch not perfused from the constant pressure reservoir decrease during induced asystole. In most dog hearts collateral channels exist between the coronary arteries and their branches. Accordingly, experiments were performed to test whether a portion of the increase of coronary inflow in the perfused coronary artery with vagal stimulation or with ventricular fibrillation arises from passage of blood to the nonperfused vessel by these channels. A total of 23 determinations on 3 animals were performed in which flow in the circumflex and descendens branches was determined following clamping of one or the other after the induction of asystole (fig. 3). As the descendens artery was clamped and its flow fell to 0, no appreciable rise occurred in the circumflex flow. The reverse was also true, that is, when the circumflex was clamped there was no appreciable rise in flow through the descendens coronary bed. Similarly, clamping of either the right coronary artery or a branch of the left coronary artery during asystole did not affect flow through the other coronary artery. Fi-

nally, occlusion of the circumflex branch following fibrillation did not significantly alter flow in the descendens branch.

It is considered unlikely that in these experiments vagal stimulation per se affected coronary inflow in any way other than by mechanical removal of myocardial contractions because, within 1 sec. or less from the onset of stimulation, coronary flow reached its new level where it was maintained during asystole. Similarly, application of electrodes to the ventricle to induce fibrillation did not appear in itself to affect coronary flow, since repeated ventricular stimulation by this means during ventricular fibrillation did not alter coronary flow.

Discussion

For nearly 3 centuries physiologists have debated the question of the direction and magnitude of the effect of ventricular systole on coronary blood flow. In 1689 Scaramucci expressed the view that the coronary vessels filled during ventricular relaxation and emptied during ventricular contraction.[2] The names of Thebesius, Vieussens, and Morgagni are associated with those who maintained that the coronary arteries are prevented from filling during systole due to closure of their orifices by the aortic valves.[3] While now all agree that the latter mechanism is untenable, there is much less certainty regarding the *net* effect of organized contraction of cardiac muscle fibers on coronary blood flow. With skeletal muscle the analogous situation is more clearly understood and the experimental results have been in closer agreement. Many observers have reported increased venous outflow during the contraction of this type of muscle. Blalock first made simultaneous observations of arterial inflow and venous drainage in the gastrocnemius before, during, and after contraction.[4] These studies clearly demonstrated a reduction in flow in the artery during contraction with a corresponding increase in venous flow. By use of the technic of direct transillumination Knisely and associates[5] have observed flow in the capillary bed of the frog and its relationship to muscular contraction. It was observed that the striated muscle fibers became wider and compressed the capillaries enough to stop flow at the beginning of a powerful contraction. As individual fibers began to relax flow began again. Studies on the myocardial vascular bed with this technic have shown compression of the capillaries by ventricular contraction to the point of erythrocyte standstill.

The importance of ventricular systole in the control of coronary flow is illustrated in a number of studies. In the left coronary artery perfused during systole at a pressure approximately equal to the prevailing mean aortic pressure, arterial inflow approaches 0.[7] Other studies have shown that for an equivalent time period, left coronary artery systolic inflow is less than diastolic inflow.[7-9] These observations lend support to the concept that organized ventricular contraction results in diminished coronary flow. However, in other studies the systolic flow in the coronary sinus has been observed to be much greater than the diastolic flow, which might suggest that ventricular systole augments coronary flow,[10] and coronary sinus drainage has been noted to decrease during ventricular fibrillation.[11] From the available data there is evident a lack of agreement as to the *net* effect of systolic contraction on flow in the coronary bed.

It is a difficult task to assess the factor of the extravascular myocardial support, and several groups of investigators have made attempts to evaluate its role in the regulation of flow in the heart-lung preparation. Various methods have been employed in an effort to clarify this problem. Hilton and Eichholtz,[12] Hammouda and Kinosita,[13] and Anrep and Hausler[14] have employed ventricular fibrillation to remove, at least in part, the effect of cardiac contraction and have determined the changes that occur in coronary flow. These investigators found that in this preparation coronary arterial inflow increased during fibrillation. In contradistinction to this, Osher[15] in studying the pressure-coronary sinus flow relationships of perfused hearts both beating and fibrillating found a decreased flow during ventricular fibrillation. Garcia Ramos[11] also noted less flow during ventricular fibrillation in the isolated mammalian heart perfused by the circulating blood of another animal. Recently Wiggers[10] has presented an evaluation of the effect of ventric-

ular contraction on coronary flow by integrating phasic flow curves recorded from the coronary sinus. Measurements were made of instantaneous flow in the coronary sinus in late diastole when the effects of myocardial compression and volume elasticity were minimal. From these data it was concluded that systole results in an augmentation in coronary flow. The validity of an analysis based upon phasic flow data rests upon the assumption that flow in the epicardial arteries and veins represents actual flow in the myocardial capillary bed. This point remains to be proved.

A method has been devised in the present studies that is thought to measure separately the magnitude and direction of the effect of mechanical ventricular activity on flow through the coronary bed and that also permits simultaneous quantitation of the vasomotor state of the coronary vessels. This method consists essentially of the simultaneous recording of blood flow in the left coronary artery and coronary sinus together with the mean coronary perfusion pressure and mean aortic pressure. The coronary system was perfused at a constant pressure approximating the prevailing mean aortic pressure and measurements were made in the normally beating heart and then during ventricular asystole induced by vagal stimulation. The possible effect of vagal stimulation per se on the coronary vessels is a factor deserving comment. Anrep[3] has shown that section of the vagi leads to an increase in coronary flow even when the heart rate is kept constant. Stimulation of the peripheral end of the vagus with rhythmically interrupted faradic current resulted in a slower heart rate with little change in coronary flow during the first 30 sec. Flow than began to diminish, reaching a minimum in 1 to 1½ min. The important point relative to the studies reported here is that vagal stimulation would not be expected to have a direct intrinsic effect on the vessel wall that would result in an *increase* in coronary flow. A flow change, if any, would presumably be opposite in direction from that following the reduction or removal of the extravascular support. For comparison, similar determinations were made before and after ventricular fibrillation and it was demonstrated that coronary flow was increased under the latter circumstances.

The induction of ventricular asystole invariably has been associated with a marked rise in coronary arterial inflow and coronary sinus drainage. The level of coronary flow reached during ventricular asystole is thought to represent that due to the vasomotor state of the coronary bed alone at the prevailing aortic pressure, and the increase in flow that occurs during asystole to indicate the magnitude and direction of the effect of myocardial contraction on blood flow through the myocardial wall. Trends of the same direction but of smaller magnitude occurred when the ventricle was in a state of fibrillation.

Summary

Coronary arterial inflow and coronary sinus drainage have been determined in the perfused heart in both the beating state and after withdrawal of the extravascular support by the induction of asystole or ventricular fibrillation. The removal of the extravascular support by this means invariably resulted in an increase in flow in the coronary arterial bed and in the venous drainage from the coronary sinus. Evidence is presented to advance the concept that the *net* effect of ventricular contraction is to impede coronary flow. Contrariwise, the removal of this factor results in an increase in flow through the myocardial vascular bed. It is believed that this approach supplies a method for the separation and quantitation of the effects on the left coronary flow of myocardial contraction and of the smooth muscle in the walls of the coronary vessels.

Summario in Interlingua

Le influxo del arteria coronari e le drainage del sino coronari esseva determinate in le corde perfundite, tanto in le stato de pulsation como etiam post le elimination del supporto extravascular per le induction de asystole o fibrillation ventricular. Le elimination del supporto extravascular per iste medio resultava invariabilemente in un augmento del fluxo in le vasculatura del arteria coronari e in le drainage venose ab le sino coronari. Es presentate datos que supporta le concepto que

le effecto *nette* del contraction ventricular es un impedimento del fluxo coronari. Inversemente, le elimination de iste factor resulta in un augmento del fluxo in le vasculatura myocardial. Nos opina que iste puncto de vista permitte le disveloppamento de un methodo pro le separation e quantitation del effectos exercite super le fluxo coronari sinistre per le contraction myocardial e per le musculo lisie in le parietes del vasos coronari.

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The earliest writings of men who later became prominent are always of great interest to those who concern themselves with the development of genius. One thinks of Osler's "Christmas and the Microscope," Lister's "Observations on the Contractile Tissue of the Iris," of Humphry Davy's "Nitrous Oxide," published when he was twenty-two, and of many others.

William Withering's medical thesis, De angina gangraenosa, published at Edinburgh when he was twenty-five years of age, is likewise peculiarly interesting because it proclaims him a keen observer and a man who had gained unusual clinical wisdom early in life.—John F. Fulton. *The Place of William Withering in Scientific Medicine.* J. Hist. Med. & Allied Sc., **8:** 16, 1953.

Arterial Homografts for Peripheral Arteriosclerotic Occlusive Disease

By MICHAEL E. DE BAKEY, M.D., E. STANLEY CRAWFORD, M.D., OSCAR CREECH, JR., M.D., AND DENTON A. COOLEY, M.D.

Sympathectomy and thrombo-endarterectomy have been largely unsatisfactory in the treatment of patients with arterial insufficiency of the lower extremities. In this paper the results are analyzed of a large experience with the use of lyophilized arterial homografts to bridge occlusive lesions below the aortic bifurcation. The criteria for selection of patients for operation, the simplified procedure of end-to-side by-pass of the obstruction, and the excellent results in 145 operations are presented.

UNTIL recently the surgical approach to chronic arterial insufficiency of the lower extremities has been an indirect attack in the form of lumbar sympathectomy.[1, 2] The rationale of this procedure lies in its release of vasoconstrictor tonus and the consequent production of the maximum degree of vasodilatation in the remaining unobstructed arterial bed.[1] It thus produces an increase in the volume of the local vascular bed and consequent improvement in the local circulation. To be sure, this change occurs primarily in the skin and not in the muscular components of the denervated part, but this is a desirable objective, since deficiency in cutaneous circulation of the feet and toes constitutes a major threat to patients with arteriosclerotic peripheral vascular disease. Gangrenous changes take place first in the skin of these parts, not in the muscle; this occurrence, rather than intermittent claudication, is the most common cause for amputation. Accordingly, improvement in blood flow through the skin with the production of dry warm feet assumes major importance.

While there can be little doubt of the benefits that may be derived from sympathectomy in chronic arterial insufficiency of the lower extremities, its limitations must also be recognized.[3, 4] For one thing it is an indirect attack upon the problem; it is not directed toward either the cause of the disease or the organic pathologic changes that have resulted from it. It is merely aimed at improvement in local circulation by producing vasodilatation in those vessels of the part, mainly the collateral vessels, that are still functionally active. For another, it is unlikely to provide significant improvement in intermittent claudication, and patients with this complaint generally persist in having considerable disability. Since sympathectomy has no effect on vessels that have already undergone obliterative structural changes and since this occlusive process usually involves the main arterial channel, it obviously cannot produce adequate restoration of circulation to relieve symptoms under these circumstances and particularly when these changes are associated with a poor collateral vascular bed.

In light of these limitations of sympathectomy and the disappointing results that often follow its use in arteriosclerotic occlusive disease of the lower extremities, efforts have been directed recently toward a better understanding of the disease. This insight had led to the development of a more direct attack upon the occlusive lesion, aimed at restoration of blood flow through the main arterial channel. This much more effective approach to the problem derives from certain pathologic and arteriographic studies by a number of observers. They have shown that the obstructing lesion in chronic arteriosclerotic occlusive

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disease of the lower extremities is frequently segmental in nature with a good sized patent segment both above and below the occlusion.[5-7] As recognized by Leriche[6] many years ago, this fortunate pathologic feature of the disease permits direct attack upon the occlusive process in reestablishing immediate arterial continuity. This possibility became a reality with the development of thrombo-endarterectomy by dos Santos[8] and others.[9] Unfortunately, the results from endarterectomy have been variable and inconsistent and the reported incidence of failures has been high.[10] In our experience postoperative thrombosis has occurred frequently and on at least 4 occasions there was sufficient interference with the existing circulation to cause ischemic changes necessitating amputation.

Bridging such defects by means of blood vessel grafts has proved more consistently successful, and the resultant improvement in circulation has been many times greater than that following sympathectomy.[11-15] Accordingly, this communication is concerned with an analysis of our experience with the use of lyophilized arterial homografts in the treatment of 145 extremities with occlusive lesions located below the aortic bifurcation.

Method and Material

Arteriography at the appropriate level is performed on all patients entering the hospital with any manifestation of arterial insufficiency of the lower extremity. Those with a patent segment of reasonable size below the obstruction and above the bifurcation of the popliteal artery are selected for operation irrespective of the length of the occlusive process above this level (fig. 1*A*). In the absence of such a patent segment, as demonstrated on the arteriogram, the graft procedure is not considered feasible and under these circumstances sympathectomy is indicated (fig. 1*B*). Secondary obstruction in the calf does not alter the results significantly, and, therefore, does not contraindicate operation. The essential requirement is the presence of a good outflow in the peripheral arterial bed as evidenced by patency of one or more of the distal branches of the popliteal artery. The presence of feebly palpable pulses does not always mean that there is no obstruction, because in several instances palpable pedal pulses have been elicited in patients with either iliac or femoral occlusion. In most of these patients, however, the pulse distal to the occlusion has been significantly weaker than that on the unobstructed side.

Fig. 1. *A*. Photograph of an arteriogram showing an occlusion of the superficial femoral artery and a normal patent segment below the occlusion. Such a case is an ideal candidate for the graft procedure. *B*. Photograph of an arteriogram showing complete occlusion of the distal superficial femoral and popliteal arteries without a patent segment distal to the occlusion of sufficient size for an anastomosis. Such a case is not a candidate for the graft operation.

Practically all patients with iliac occlusion surveyed in this manner have been candidates for operation. Among the patients with femoral occlusion, however, the incidence of operability was somewhat less and has varied with the clinical manifestations of arterial insufficiency. In those, for example, in whom intermittent claudication was the only indication of inadequate circulation, an operable distal segment has been found in about 75 per cent of the cases, while in patients with inadequate circulation at rest, the incidence of operability has been approximately 55 per cent. It would appear, therefore, that patients with high obstructive lesions involving the iliac arteries near the aortic bifurcation are more likely to have a well localized atherosclerotic occlusive process with a good peripheral arterial bed, whereas those with peripheral lesions tend to have more diffuse arteriosclerotic occlusive disease.

Operability in the diabetic patient is not appreciably different from that in the nondiabetic individual; when the same criteria of selection are applied to these patients, the degree of operative

success has been the same. Eight patients with Buerger's disease have been surveyed by arteriography and none has proved to be a candidate for operation.

Most patients found to be candidates for operation have had grafts inserted. The few patients with operable lesions not subjected to operation had advanced cardiac or renal disease and the associated intermittent claudication was not considered sufficient indication to justify the risk of surgical intervention. On the other hand, when loss of limb was probable, the risks of the graft procedure were usually accepted inasmuch as this operation was considered a substitute for amputation. In our experience, patients have tolerated peripheral grafting procedures considerably better than either sympathectomy or amputation. This difference is undoubtedly due to the reduction in trauma and the use of immediate ambulation of these older patients with generalized arteriosclerosis.

TABLE 1.—*Results in 145 Operations in which Homografts Were Employed to Replace or By-Pass Arteriosclerotic Occlusive Lesions of the Lower Extremity*

Type of operation	Location of occlusion	Number of operations	Patent grafts	
			Number	Per cent
Excision and graft	Iliac	18	17	95
	femoral	12	9	75
End-to-side by-pass	Iliac	61	57	93
	femoral	54	47	87
Total		145	130	90

The indication for operation in most of these patients has been intermittent claudication, which was frequently disabling. Fifteen patients had gangrene of limited degree, and 1 had extensive gangrene. Five patients had painful ischemic ulcers, 29 had severe rest pain, and in 1 a digit had been destroyed by associated infection. Operation was advised in the patient with extensive gangrene to permit a low leg amputation, since the opposite leg had been amputated previously at a higher level.

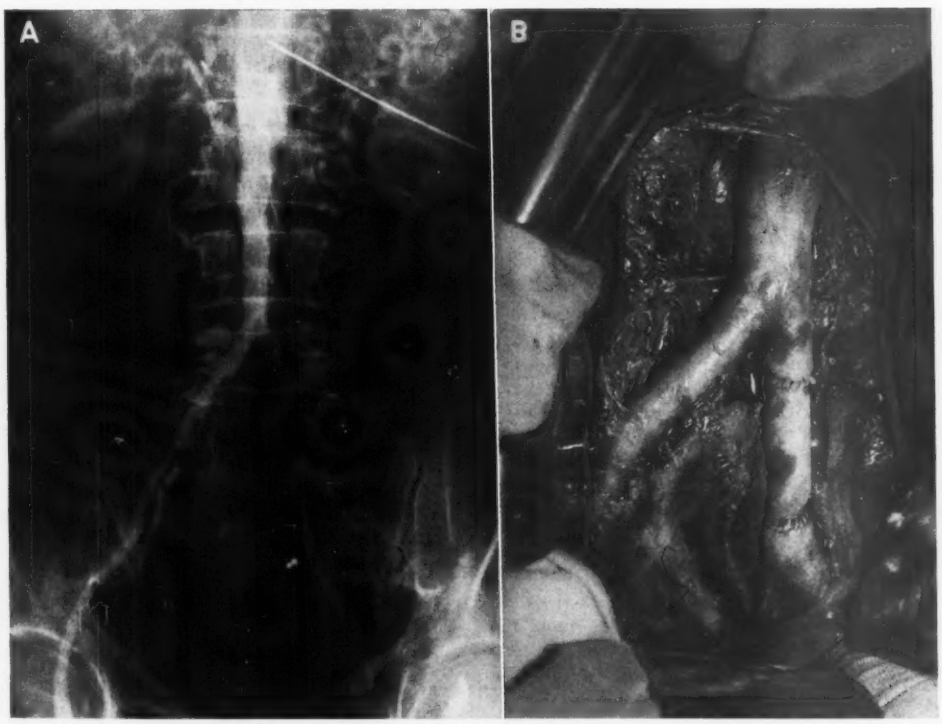

FIG. 2. *A*. Photograph of an aortogram showing an occlusion of the left common iliac artery. *B*. Photograph at operation showing the graft in place after excision of the occluded iliac segment.

FIG. 3. Photograph taken at operation showing an arterial homograft inserted by an end-to-side anastomosis to the left common iliac artery above and to the left common femoral artery below to by-pass an occlusion of the left external iliac artery.

The 145 cases in this series were analyzed according to the 2 methods of grafting procedures employed, i.e., excision of the occluded segment with graft replacement and the end-to-side by-pass procedure without excision of the diseased segment. In addition, the series was analyzed according to the site of occlusion (table 1). An additional 194 cases of occlusion of the iliac artery associated with the Leriche syndrome or thrombo-obliterative disease of the distal aorta and bifurcation were excluded from this series. In these cases a part of the iliac artery was resected, and frequently the short remaining occluded segment was endarterectomized. The bifurcation aortic homograft was then anastomosed to this endarterectomized distal iliac segment with highly gratifying results.[16] Also excluded were the cases of femoral occlusion treated by endarterectomy, vein graft, heterograft, and synthetic prosthesis.

Technic of Operation

While the primary objective of operations is to restore a normal pulsatile blood flow into the peripheral arterial bed, it should also be the purposes of the operation to minimize recurrence of the disease and to prevent reduction in the existing circulation in the event of graft failure. It is essential, therefore, to bridge the entire occluded segment including all areas of proximal or distal narrowing of the artery; no patent channel, either in the diseased arterial segment or in any collateral vessel, should be sacrificed. Accordingly, the short discrete occlusive segment may be completely excised and replaced by a graft, but longer occlusive segments or those with stenosis or narrowing above or below the area of complete obstruction are preferably treated by the by-pass operation. In our series, for example, there were 30 extremities in which the occlusive lesions were less than 15 cm. in length and all of these were completely excised and replaced by arterial homografts (fig. 2). In the other 115 cases the occlusive areas were longer, multiple, or inconveniently located for excision, so that the by-pass procedure was employed as originally proposed by Kunlin.[17] This by-pass is accomplished by performing an end-to-side anastomosis between the graft and the host artery both above and below the site of occlusion (fig. 3). Usually, 2 small incisions are made that are connected by a tunnel through which the graft extends from one anastomosis to the other (fig. 4). The technical details of the by-pass procedure have been presented elsewhere.[3]

RESULTS

Successful restoration of blood flow distal to the site of occlusion following operation was determined by arteriography or by the presence of palpable pulses below the level of occlusion not felt before operation. Of the 145 extremities treated, a distal pulsatile blood flow was successfully re-established in 130 (90 per cent) (table 1). The failures followed excision and grafting in 4 patients, 1 of whom had an iliac occlusion and 3 femoral artery occlusions. The by-pass procedure failed in 11 patients, 4 of 61 iliac artery and 7 of 54 femoral artery occlusions. These 11 failures were associated with complete distal femoral arterial occlusions in the 4 iliac artery failures; in the 7 femoral occlusions in which the graft did not remain open, the distal patent segment was small and its outflow was so reduced that thrombosis occurred during or soon after operation. The possibility of failure in these

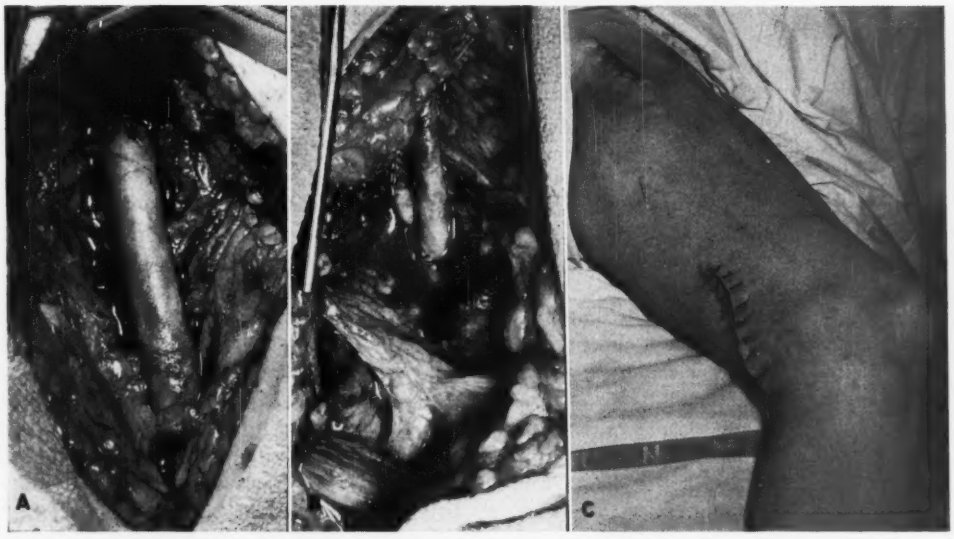

FIG. 4. Photograph taken at operation showing an arterial homograft inserted by an end-to-side anastomosis to (*A*) the left common femoral artery above and (*B*) the popliteal artery below to by-pass a long occluded segment of the superficial femoral artery. (*C*) Location of the 2 incisions employed in this case.

cases was anticipated but operation was attempted in the hope that some increase in blood flow could be obtained. These cases must now be regarded as errors in selection. The arterial circulation in 2 of the 3 femoral arterial excisions and graft failures was made worse by the operation and amputation was subsequently necessary in both these extremities. Particularly significant is the fact, however, that none of these patients who had the by-pass procedure was made worse by the operation.

There was striking improvement in peripheral circulation in those extremities in which the grafts remained patent. Intermittent claudication, rest pain, and pain from ischemic ulceration were immediately and completely relieved in all patients. The ischemic ulcers healed rapidly and the mild gangrenous changes quickly disappeared. The gangrenous infected toe was amputated and the open stump quickly healed. In the patient with extensive gangrene of the foot associated with ischemic changes extending into the thigh, a low leg amputation stump successfully healed following a by-pass graft that re-established a pulsatile circulation down to the ankle. In view of the previous mid-thigh amputation of the other leg, the additional length of this stump afforded by the graft has been of distinct advantage in the rehabilitation of the patient.

Even though most of these operations were done during the past 18 months, a considerable number was performed as long as 2½ years ago. All patients have been carefully followed since discharge and only 2 have had recurrence of symptoms, which in both instances was associated with thrombosis of the graft. One patient had had bilateral intermittent claudication associated with occlusions of the aorta, both iliac and right superficial femoral arteries. The aorta and left common iliac artery were replaced by a homograft and the right iliac and femoral occlusions were by-passed with a homograft extending from the aortic homograft to the popliteal artery. This patient was completely relieved of symptoms after operation and strong pulses appeared throughout both extremities. After discharge from the hospital the patient returned to work and was asymptomatic for 14 months, at which time intermittent claudication returned in the right

leg. This change was associated with the loss of pulses throughout the extremity and a reduction in circulation only equal to that found before operation. The second patient had had a right femoral by-pass graft inserted because of intermittent claudication, severe rest pain, and early gangrenous changes of the toes, which ordinarily constitute adequate indication for low thigh amputation. After operation, pedal pulses were restored with immediate relief of symptoms and rapid regression of the skin changes. This improvement continued until intermittent claudication returned 11 months later. The pulses, which were previously present, could no longer be palpated, but there were no gangrenous changes or rest pain. The distal circulation at this time was considerably better than prior to operation, and regardless of late occlusion of the graft in this case, the emergency period in the circulation of this extremity had been relieved.

Complications

There were 2 deaths in this series due to acute myocardial infarction occurring during operation. One of these patients had an iliac occlusion associated with a large leaking abdominal aneurysm that required emergency operation. The iliac occlusion was treated by insertion of a homograft end-to-side from the common femoral artery to the bifurcation aortic homograft. Had this patient not had rupture of the aneurysm, he would not have been selected for operation in view of his known heart disease. In the other patient who died of coronary occlusion, the complication developed during a second operation performed to control bleeding from a suture line where 2 short homografts had been united to form a long one. This patient probably would have survived and would have been completely rehabilitated had this initial complication not occurred.

A superficial wound infection developed in 1 patient and another had thrombophlebitis associated with a small pulmonary infarct, but both recovered completely without residual disturbances. The single major amputation performed following a by-pass graft was for a part that was destroyed prior to hospital admission. The preoperative circulation was unaltered in the 11 by-pass failures. In the group having excision and graft the circulation of 2 extremities was severely impaired by an unsuccessful operation so that amputation was later required.

Discussion

The results obtained in these patients have been extremely gratifying. In our experience these results are far superior to other operations, particularly lumbar sympathectomy. It has been a rewarding experience to observe gangrenous changes regress almost overnight and older patients with severe disabling symptoms resume their normal activities. The few poor results were due to errors in selection of patients for operation.

On the basis of this experience several factors assume major importance in contributing to the gratifying results obtained from this method of therapy. These include particularly the proper selection of cases, the use of freeze-dried arterial homografts, and, perhaps above all, employment of the simplified technic of the end-to-side by-pass procedure.

As emphasized previously, there are 2 important considerations in the selection of patients for operation. The first is concerned with the risk to life and limb. Obviously in the patient with severe impairment of cardiac or other vital function who has only intermittent claudication, operation may be contraindicated not only because of the increased risk, but also because under these circumstances the patient's activities will not be altered by improvement in circulation of the extremities. On the other hand, in patients with occlusive lesions that threaten loss of the extremity, operation may be indicated on the basis that they can withstand the grafting procedure, which might preserve the extremity, as easily as, if not more easily than, an amputation.

The second consideration in the proper selection of patients for operation is concerned with the presence of an adequate patent peripheral arterial bed below the occluded segment for the ready outflow of blood. This can be readily established by proper arteriographic

studies, which should demonstrate not only the limits of the occlusive process, but also the character of the arterial bed well beyond the distal point of the occlusion.

The availability of arterial homografts, preserved by the freeze-drying process, has undoubtedly contributed significantly to the successful application of this method of therapy. The advantages of this type of blood vessel graft are numerous, including particularly ease and simplicity of preparation, assurance of general uniformity of caliber, and facility in technical performance of anastomosis.

The end-to-side by-pass operation is undoubtedly a highly important, if not the most important, factor that has contributed to the success of direct surgical attack in these cases. It is based upon the natural response of the arterial bed to occlusion, that is, development of collateral vessels around the obstructed area. Thus, the operation consists essentially in the addition of an artificial collateral artery around the obstruction, which, being as large as the host vessel, assures immediate maximum restoration of a distal pulsatile blood flow.

The technical features of the operation, like its conception, are simple. The small incisions require minimal dissection; thereby injury to adjacent structures is reduced. The host artery is only slightly disturbed and no collateral branch is sacrificed (fig. 5). The most normal section of host artery both above and below the occlusion can be selected for anastomosis, irrespective of the intervening distance and without fear of jeopardizing existing collateral circulation or increasing significantly the extent of operation. If the procedure fails to restore normal circulation, or if the graft becomes occluded later, it does not alter the circulation already present in the leg. In addition to these technical advantages, a high degree of success has been obtained without significant complications and with minimal risk to life and limb.

In the early phase of this study, it was thought that relatively short occlusive segments might be best treated by excision and graft replacement. As experience was gained with the by-pass procedure, however, and its distinct advantages in simplicity of performance and in providing a high degree of success with minimal risk became more apparent, it has become the procedure of choice in our hands even in cases with relatively short occlusive lesions.

FIG. 5. Photograph of a right femoral arteriogram after operation showing a functioning end-to-side by-pass graft. Note the lack of disturbance to the obstructed host artery and its collateral vessels.

This experience has also led us to abandon

the use of lumbar sympathectomy as a supplemental procedure as was done routinely in our earlier cases. It is now employed only in cases in which the occlusive process is not associated with a patent distal segment (fig. 1*B*). Of particular interest is the fact that lumbar sympathectomy had been previously performed on 19 of the patients in this series, none of whom obtained adequate relief of symptoms. Following the grafting procedure all were completely relieved of their manifestations of arterial insufficiency.

Finally, and of particular importance, is the impressive fact that this form of therapy is applicable in the majority of patients with arteriosclerotic arterial insufficiency of the lower extremities, which is by far the most common type of peripheral vascular disease. This wide applicability is well illustrated by observations derived from our experience with this method of study during the past several years. Thus among all cases examined and found on arteriography to have iliac occlusion, virtually all proved to be candidates for operation and successful results were achieved in 93 per cent of these cases. Although this incidence of operability was somewhat less among patients with femoral occlusions, it is noteworthy that well over one half of them were found to be candidates for operation and successful results followed operation in 87 per cent of the cases. It is thus apparent that this form of management not only provides a high degree of success but also may be employed in the majority of patients with arterial insufficiency of the lower extremities.

Summary

Results of indirect methods of treating peripheral arterial insufficiency of the lower extremities have been generally disappointing. The response in any 1 case has been difficult to predict. Rest pain and intermittent claudication are relieved infrequently. Sympathectomy has offered little or no absolute certainty against amputation for many of the manifestations of arterial insufficiency.

Arteriographic studies on patients with chronic arterial insufficiency of the lower extremities have demonstrated that the occlusive lesion is localized and discrete with a patent vessel above and below it in the majority of instances. As a consequence of this pathologic feature of the disease, it is possible to restore distal circulation immediately in most of these patients by direct surgical means and thus assure immediate relief of symptoms, healing of cutaneous lesions, and prevention of amputation. Several methods of direct attack have been devised, the most consistently successful of which has consisted in substitution of an arterial homograft for the obstructed segment.

This procedure may be accomplished by either of 2 technics. The occlusion may be completely excised and replaced by a graft, or a graft can be used to by-pass the occlusion by suturing the graft end-to-side both above and below the occlusion. In the early phases of this study the former method was used in short discrete lesions and the latter for longer occlusive segments. More recently, and because the end-to-side by-pass procedure has proved superior, it has been employed almost exclusively.

These procedures were employed in 145 extremities for occlusion, 79 of which involved the iliac and 66 the femoral artery. Excision and grafting were performed in 30 extremities, 18 with iliac and 12 femoral arterial occlusion. The by-pass procedure was used in 115 extremities, 61 of which had iliac and 54 femoral arterial occlusion. A pulsatile blood flow distal to the occlusion was successfully restored and all symptoms were relieved in 90 per cent of the cases. Approximately 15 to 20 per cent of these patients were candidates for immediate or early amputation. This procedure was prevented in all but 1 patient whose foot had already been destroyed prior to operation.

There were 2 hospital deaths from coronary thrombosis, and 2 low thigh amputations were required following failure of excision and grafting. The circulation was not affected in any of the 11 patients in whom the by-pass operation was unsuccessful.

Summario in Interligua

Le resultatos de indirecte methodos de tractamento de peripheric insufficientia arterial del

extremitates inferior es generalmente disappunctante. Le responsas in le specific caso individual es difficile a predicer. Dolor de reposo e claudication intermittente es alleviate infrequentemente. Sympathectomia offere pauc o nulle absolute certitude del obviation de amputation pro multes del manifestationes de insufficientia arterial.

Studios arteriographic de patientes con chronic insufficientia arterial del extremitates inferior ha demonstrate que le lesion occlusive es localisate e discrete con un vaso patente supra e infra su sito in le majoritate del casos. Como consequentia de iste characteristica pathologic del morbo, il es possibile restaurar le circulation distal immediatemente in le majoritate de iste patientes per directe medios chirurgic, con consequente assecurantia del immediate alleviamento del symptomas, de curation de lesiones cutanee, e del obviation de amputationes. Varie methodos de attacco directe ha essite disveloppate. Inter illos le plus uniformemente succedente ha consistite in le insertion de un homograffo arterial in loco del segmento obstruite.

Iste manovra pote esser executate in un de duo manieras. Le occlusion pote esser completemente excidite e reimplaciate per un graffo, o le graffo pote esser usate in contornar le occlusion per suturar lo termino-a-pariete supra e infra le occlusion. Durante le prime phases del presente studio le methodo a excision complete esseva usate in curte lesiones discrete, e le methodo a derivation esseva usate in casos de occlusion de plus longe segmentos. Plus recentemente, le methodo a suturation termino-a-pariete se ha provate superior e ha essite usate quasi exclusivemente.

Iste manovras esseva empleate in 145 extremitates con occlusion arterial. In 79 casos le arteria iliac esseva implicate; in 66 casos il se tractava del arteria femoral. Excision e graffo esseva empleate in 30 extremitates, 18 con occlusion del arteria iliac, 12 con occlusion del arteria femoral. Le methodo a derivation esseva empleate in 115 extremitates, 61 con occlusion del arteria iliac, 54 con occlusion del arteria femoral. Un fluxo pulsatile de sanguine distal al occlusion esseva restaurate con bon successo e omne le symptomas esseva alleviate in 90 pro cento del casos. Circa 15 a 20 pro cento de iste patientes esseva candidatos pro immediate o imminente amputationes. Le amputationes esseva evitate in omne casos, con un exception. In isto, le pede esseva jam destruite ante le operation.

Occurreva in le serie 2 mortes hospitalari ab thrombosis coronari. Duo amputationes inferofemoral esseva requirite post non-successo de excision con graffo. Le circulation non esseva afficite in ulle del 11 patientes in qui le operation a derivation non succedeva.

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Hypertension is defined by its negative characteristics and is identified by exclusion. It represents a group of individuals with elevated blood pressure without a discoverable causal lesion. Because of the practice of differentiating normal blood pressure from elevated blood pressure, the concept has developed that essential hypertension is a specific pathologic entity with a single and unitary cause. Hypotheses in regard to the nature of its cause are numerous. Examination of the evidence on which the current concepts are based demonstrates that this concept is not justified. In the general population, distribution curves of the frequency of blood pressure demonstrate a continuous variation. The observed facts do not justify the differentiation of the population on the basis of the blood pressure. If there exists a group in which the blood pressure does not increase with advancement in age, it would seem that this represents a very small group, and to designate such individuals as having normal blood pressure would seem to be a wrong terminology. It has frequently been proved that the malignant phase follows as a direct consequence of the intensity of the hypertension and of the rapidity with which the blood pressure rises. The malignant phase can be reverted to the benign phase by various medical therapeutic procedures. Also, the differentiation between normal blood pressure and the benign and malignant phases of high blood pressure is fundamentally of a quantitative rather than a qualitative character. The malignant phase of hypertension forms a compact clinical group because it reflects a well-defined vascular lesion, acute fibrinoid arteriolar necrosis, with a relatively well-defined cause. By contrast, the benign phase is extremely heterogeneous and merges imperceptibly into the population at large. This is true because the chief vascular abnormalities of the benign phase are found also in those subjects with lower pressures though they are probably less frequent and less severe and carry a smaller hazard. The chief risk, heart failure, is probably, at least in part, a consequence of the height of the arterial pressure, for there is now little doubt that if an initially grossly raised arterial pressure is lowered by sympathectomy or hypertensive drugs, the heart failure may resolve. The arterial lesions of the benign phase more specifically associated with hypertension, i.e., elastosis and fatty hyaline thickening of arterioles, have not been produced experimentally but may represent the effects of high blood pressure; their clinical consequences would, however, seem relatively unimportant. Arterial disease and high blood pressure are phenomena of different orders and should not be confused. It is the height of the blood pressure that matters. It is not intended to imply that arterial disease is unimportant. Arterial disease is, in most of us, of much greater moment than the height of the arterial pressure, but its study presents a peculiar difficulty, i.e., that of determining its presence, extent, and type prior to the occurrence of vascular catastrophe or the death of the patient. The important arterial lesions in the benign phase of hypertension also occur in patients with lower blood pressure though perhaps less frequently and less severely. The intensity of the hypertension is clearly a factor in the production of hypertensive heart failure. The phenomena of the malignant phase are consequences of an extremely severe hypertension. A study of the clinical features of essential hypertension supports the idea that blood pressure behaves as a graded characteristic, increasing the severity or the risk of certain disorders of large arteries, increasing the load on the heart and when it exceeds a certain threshold, precipitating acute fibrinoid arteriolar necrosis, which is the basis of the malignant phase.

Wendkos

Differential Effect of Dietary Fat and Weight Reduction on Serum Levels of Beta-Lipoproteins

By WELDON J. WALKER, M.D., NORMAN WEINER, M.D., AND LAWRENCE J. MILCH, PH.D.

Twenty-five patients sustained an average weight loss of 21.7 pounds on a diet in which 73 per cent of total calories consisted of animal fat. Their "new" weight was maintained on this high-fat diet and subsequently on a low-fat diet. Standard S_f 0-12 lipoproteins were highly influenced by dietary fat intake independent of weight change. In contrast the S_f 20-400 fraction was lowered by negative caloric balance and weight reduction despite the ingestion of large amounts of animal fat. These changes were statistically highly significant. Divergent responses of different classes of beta-lipoproteins may be missed if only total beta-lipoprotein measurements are made.

IT IS generally agreed that in man there is at least a rough correlation between the incidence of atherosclerosis and high levels of serum cholesterol and various classes of lipoproteins, particularly the beta-lipoproteins.[1, 2] Insurance studies demonstrate that obesity is associated with human atherosclerosis, since insured overweight individuals have an increased death rate from coronary artery disease. This increased mortality fails to occur if obese individuals reduce their weight.[3] Greatest longevity is encountered in individuals approximately 15 per cent underweight.[4] Love and Walker[5] found that in 1,000 individuals between 30 and 60 years of age there was a significant increase in both serum cholesterol and S_f 12-20 lipoprotein levels with increasing weight. A significant lowering of various classes of lipoproteins with weight reduction has been reported in 39 patients with coronary artery disease who ingested a high-cholesterol, low-fat diet.[6] An association between caloric balance and serum lipoproteins was suggested by the observation that forced feeding of a low-fat, low-cholesterol diet resulted in increased lipoprotein concentrations in volunteer subjects.[6] However, Keys contended that the quantity of dietary fat is the most important factor associated with elevation of serum cholesterol levels and the development of atherosclerosis in the human. He stated that obesity is a relatively unimportant factor in human atherosclerosis.[7]

With such divergent views it seemed desirable to study the effect of weight reduction on the serum lipoprotein levels in a group of patients ingesting a high-fat diet. It appeared advantageous to conduct such a study on a group of individuals many of whom had manifested atherosclerosis relatively early in life, since this disease process may in some measure represent an alteration in the homeostatic mechanisms controlling cholesterol metabolism. Such individuals might be more responsive to factors tending to elevate or depress serum lipoprotein levels.

METHODS AND MATERIAL

Twenty-five patients were studied. Eighteen had proved atherosclerosis, 17 having sustained 1 or more myocardial infarctions, while the eighteenth had thrombosis of the left common iliac artery. Twenty-three were males, 2 were females. Their ages varied from 33 to 66 years and the average age was 46 years. All patients were studied in the Cardiovascular Service, Brooke Army Hospital. The majority were studied as outpatients. No one with an acute myocardial infarction was included in the study. All blood samples were taken in the fasting state. Patients had 2 control determinations at intervals of at least 1 week while maintaining their weight constant and ingesting their accustomed diets. Six patients had been on a low-fat diet prior to the study; the remainder were eating what was considered an average American diet.

Following the second control determination patients were started on a regimen of weight reduction consisting of a high-fat, high-meat diet as described by Pennington.[8] At each meal the subjects received a 6- to 8-ounce serving of meat (1 part of fat to 3 parts of lean by weight). In addition,

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patients were allowed 1 small serving of fruit or vegetable at each meal. They were allowed coffee or tea ad lib., without added sugar or cream. If the patient was still hungry at the end of the meal he was allowed additional meat but no additional fruit or vegetable. On such a diet the daily fat intake was estimated to be at least 200 Gm. and constituted approximately 73 per cent of the total caloric intake; protein approximately 17 per cent of total calories; and carbohydrate about 10 per cent of total calories. Patients received a daily multivitamin capsule. No one complained of ill effects other than developing a distaste for meat. The minimum weight loss was 12 lb.; the maximum 48 lb. There was an average weight loss of 21.7 lb. The average rate of weight loss was 1.6 lb. per week.

After the period of weight reduction, total calories were increased on the same high-fat diet so as to maintain a constant weight. This new regimen was continued for a minimum of 1 month and in the majority of cases for 2 months.

Finally the diet was changed to one of less than 50 Gm. of fat per day. This diet contained at least 1 Gm. of protein per Kg. body weight and the calories were adjusted so as to maintain a constant weight. Most subjects were continued at least 2 months on this diet—all for at least 1 month.

Lipoprotein determinations were ordinarily made at 2-week intervals during the entire period of the study. Lipoprotein determinations were done at the School of Aviation Medicine, Randolph Air Force Base, Tex. Standard S_f 0-12, 12-20, and 20-400 classes of β-lipoproteins were determined on each specimen.[9, 10] Serum cholesterol determinations were done in the clinical laboratory at Brooke Army Hospital, Fort Sam Houston, Tex. A change in the method of determining serum cholesterol occurred during the period of the study, and these results are therefore not reported. The data were analyzed by M. Bryan Danford, Ph.D., Analytical Statistician, School of Aviation Medicine, Randolph Air Force Base, Tex.*

* An analysis of variance was performed on the data, by standard F-ratio tests for assessing statistical significance of various main effects (subjects, diets, types of patients). Further testing was performed by using Student's t. (See Cochran, William G., and Cox, Gertrude, M. Experimental Designs. John Wiley & Sons, Inc., New York, 1950).

During the various diet periods, control, high fat-weight loss, high fat-weight maintenance, and low fat-weight maintenance, from 2 to 8 measurements were made on each individual. In tables 1 and 2, the standard errors of the means represent measures of variability of the means as taken over people as well as over the several observations made on each person. Thus if N persons are measured k times, the standard error of the mean is $\sigma/\sqrt{kN}$, when σ^2 is the mean square for persons or σ^2/k is the variance among the means for the N persons.

Results

In preliminary analysis the 18 patients with manifest atherosclerosis were separated from the 7 who did not have proven atherosclerosis. The average ages of the 2 groups were 47 and 44 years respectively. As indicated in table 1 the initial levels of all classes of lipoproteins appeared significantly higher in the group with manifest atherosclerosis ($p < .05$). Both groups showed the same general response to the dietary regimens and are combined in subsequent analyses. However, patients with manifest atherosclerosis tended to show a greater response to the changing dietary schedules than those without proven coronary

TABLE 1.—*Comparison of Mean Control Serum Lipoprotein Levels in Subjects with and without Atherosclerosis*

Class of lipoprotein	Manifest atherosclerosis (18 subjects)	No evident atherosclerosis (7 subjects)
S_f 0-12 (mg.%)	426 ± 20.8	373 ± 33.4
S_f 12-20 (mg.%)	59 ± 4.9	44 ± 7.8
S_f 20-400 (mg.%)	178 ± 17.4	127 ± 27.9

From 1 to 2 measurements were made on each subject.

There was a significant difference between mean control values of all classes of lipoproteins in the patients with manifest atherosclerosis as compared with those without evident atherosclerosis, $p < .01$ for S_f 0-12 and $p < .05$ for S_f 12-20 and S_f 20-400.

TABLE 2.—*Mean Values of Serum Lipoproteins as Influenced by Dietary Fat Intake and Weight Reduction*

Class of lipoproteins	S_f 0-12 mg.%	S_f 12-20 mg.%	S_f 20-400 mg.%
Control	411±12.4	54±2.6	164±9.5
During period of weight loss on high-fat diet	451±10.3	58±2.2	118±7.8
Maintaining "new" weight on high-fat diet	444±11.8	52±2.5	119±9.0
Maintaining "new" weight on low-fat diet	395±10.3	48±2.2	120±7.8

Number of subjects measured was 25. From 2 to 8 measurements were made on each subject for each diet condition, standard errors indicated.

Changes in the S_f 0-12 and S_f 20-400 classes of lipoproteins were highly significant, $p < .01$. Whereas the S_f 0-12 class was well correlated with dietary fat intake, the S_f 20-400 lipoproteins were more responsive to weight reduction.

disease. Previous studies have suggested that either positive or negative caloric balance may influence serum lipoprotein levels.[6] Hence, determinations made during the period when patients were losing weight on a high-fat diet were analyzed separately from data obtained when patients were ingesting a high-fat diet and maintaining their weight constant at the "new" reduced level. As shown in table 2, when patients consumed a high-fat diet, there was a highly significant ($p < .01$) elevation of the S_f 0-12 class of lipoproteins as compared with control levels, in spite of the fact they were losing weight. This increase was maintained as long as they remained on a high-fat diet. When the diet was changed to one of low fat, the serum concentrations of S_f 0-12 lipoproteins decreased significantly to below control levels.

The S_f 12-20 lipoprotein class showed changes that were significant at the 5 per cent level ($p < .05$). However, the mean values on the dietary regimens were so closely grouped as to require that any interpretation be viewed with caution.

The response of the lipoprotein S_f 20-400 fraction was in marked contrast to that observed for the higher density lipoproteins. There was a highly significant ($p < .01$) reduction in the S_f 20-400 fraction soon after patients were in negative caloric balance, regardless of the amount of fat in the diet. The depression of this lipoprotein class persisted when the diet was changed from high fat to low fat as long as the "new" low weight level was maintained.

Discussion

A significant body of data has been accumulated that indicates a high correlation between elevated serum β-lipoprotein concentrations and the development of coronary artery disease. Our data indicate that weight reduction and dietary fat content produce different effects on at least 2 of the β-lipoprotein classes. Thus, significant changes may be obscured or entirely missed if an investigator measures only total β-lipoprotein or total serum cholesterol levels.

The relative importance of the various classes of lipoproteins in the genesis of atherosclerosis is not definitely established. In our study, whereas the S_f 0-12 lipoprotein class was well correlated with dietary fat content, the S_f 20-400 class was more responsive to weight reduction. Such correlations, however, do not assess the relative importance of obesity versus dietary fat intake as causal factors in the genesis of human atherosclerosis. It is probable that both factors are important and the data presented lend support to this view.

Summary

The effect of dietary fat intake and weight reduction on levels of the various classes of serum lipoproteins was determined in 25 human subjects. The majority of patients had proven coronary artery disease. During the first period of the study, the patients sustained an average weight loss of 21.7 pounds while on a diet in which approximately 73 per cent of total caloric intake consisted of animal fat. Following this period of weight loss the patients' weights were maintained constant while they continued to ingest this high-fat diet in increased quantities. Finally, subjects were maintained at a constant weight on a diet containing less than 50 Gm. of fat per day. Standard S_f 0-12 and S_f 20-400 classes of β-lipoproteins showed a completely dissimilar response. The serum levels of the S_f 0-12 fraction were highly influenced by dietary fat intake rising on a high-fat diet and falling on a low-fat diet, apparently independent of weight change. In contrast the S_f 20-400 fraction was significantly lowered by negative caloric balance and weight reduction, despite the ingestion of large amounts of animal fat. These changes were statistically highly significant ($p < .01$). The S_f 12-20 class of lipoproteins showed less striking responses to weight reduction and dietary fat intake. These data lend support to the concept that body leanness and restriction of dietary fat may both be important in preventing human atherosclerosis. In addition, divergent responses of different classes of β-lipoproteins to various dietary and nutritional regimens may be entirely missed if only total β-lipoprotein or total cholesterol measurements are made.

Summario in Interlingua

Esseva determinate in 25 subjectos human le effecto del ingestion dietari de grassia e del reduction de peso super le nivellos del varie classes de lipoproteina seral. Le majoritate del subjectos esseva patientes con demonstrate morbo de arteria coronari. Durante le prime periodo del studio, le patientes experientiava un perdita medie de peso de 21.7 lbs. A iste tempore lor dieta includeva grassia animal amontante a circa 73 pro cento del total ingestion caloric. Post iste periodo de perdita de peso, le pesos del patientes esseva mantenite a nivellos constante durante que le dieta con le mentionate alte procentage de grassia esseva ingerite in augmentate quantitates. Finalmente, le subjectos esseva mantenite a nivellos constante de peso con un dieta continente minus que 50 g de grassia per die. Le classes standard S_f 0–12 e S_f 20-400 de lipoproteina beta monstrava responsas completemente dissimile. Le nivellos seral del fraction S_f 0-12 esseva grandemente influentiate per le ingestion dietari de grassia. Illos montava con un dieta ric in grassia e descendeva con un dieta povre in grassia, apparentement sin dependentia del alterationes de peso. Del altere latere, le fraction S_f 20-400 esseva significativemente reducite per un negative balancia caloric e reduction de peso, in despecto del ingestion de grande quantitates de grassia animal. Iste alterationes esseva de grande signification statistic ($p < 0{,}01$). Le classes S_f 12-20 de lipoproteina monstrava minus frappante responsas al reduction de peso e al ingestion dietari de grassia. Iste datos supporta le conception que magritate del corpore e restriction del grassia dietari pote ambes esser de importantia in prevenir atherosclerosis human. In plus, divergente responsas de differente classes de lipoproteina beta a varie regimes nutritional e dietari pote escappar completemente al observation si solmente mesurationes total de lipoproteina beta o de cholesterol es executate.

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The scientist does not study nature because it is useful. He studies it because he delights in it, and he delights in it because it is beautiful.—Henri Poincaré, 1854–1912.

Primary Pulmonary Hypertension

Review of Literature and Results of Cardiac Catheterization in Ten Patients

By Don W. Chapman, M.D., Jack P. Abbott, M.D., and Joseph Latson, M.D.

A brief historical review of primary pulmonary arteriosclerosis and hypertension has been given. Ten additional cases with detailed laboratory, roentgenographic, electrocardiographic, cardiac catheterization, and angiocardiographic studies are presented. The findings on 4 necropsied cases are also included. Progressive exertional shortness of breath, syncope, left chest pain, right ventricular hypertrophy, and pulmonary arterial dilatation, combined with high right ventricular and pulmonary arterial pressure and normal pulmonary capillary pressure in the absence of pulmonary disease, should be extremely suggestive of primary pulmonary hypertension. An unrelenting downhill course of right ventricular failure is usually seen.

PRIMARY pulmonary hypertension has been considered a rare disease. This paper is presented for the purpose of adding 10 cases to the literature and discussing the differential diagnosis and pathology. An attempt will be made to discuss the outstanding features of the cases presented with regard to similarities and differences in the literature. The patients in this series have been studied by clinical evaluation, routine laboratory procedures, electrocardiographic tracings, teleroentgenograms, cardiac catheterization, lung biopsy in 1 case, necropsy examination in 4 cases, angiocardiography in 2 cases, and miscellaneous clinical procedures such as circulation times, venous pressures, and pulmonary function studies.

Because of sharp conflicts of opinion in the literature, it is very difficult to know the frequency with which the disease occurs. As with many rare diseases, the discrepancy in reporting has been due in part to the numerous synonyms and variance in the criteria for diagnosis. Ayerza's disease, Ayerza's syndrome, idiopathic pulmonary hypertension, arteriosclerosis of the lesser circulation, idiopathic right ventricular hypertrophy, cardiacos negros, "black cardiac disease," pulmonary Raynaud's disease, and many other names have been applied to the disease.

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Review of Literature

Sclerotic plaques in the pulmonary arteries were noted by Vieussens[1] in 1709, but their presence is not necessarily diagnostic of primary pulmonary arteriosclerosis in view of present concepts of the disease. Brenner[2] reported in 1935 that 23 of 31 routine autopsies showed some pulmonary vascular sclerosis, but only 1 case showed right ventricular hypertrophy and had circulatory symptoms. Moschcowitz[3] reported varying degrees of pulmonary arteriosclerosis in 6.5 per cent of 770 consecutive necropsies. Ayerza,[4] in 1901, described a patient with severe cyanosis who at autopsy had right ventricular hypertrophy and chronic bronchitis, but he did not mention any pathology in the pulmonary vessels. It was because of a doctoral thesis by Marty[5] in 1912, and subsequent articles by Arrillaga,[6] and Escudero[7] that the term "Ayerza's disease" became popular. These 3 men were former students of Ayerza, and besides popularizing that term, they focused attention on obliterative disease of the pulmonary vessels, which they attributed to syphilis. In 1891 and 1892, Romberg[8] and Aust[9] described the clinical picture of pulmonary hypertension and ascribed it to pulmonary sclerosis found grossly at necropsy. However, they did not demonstrate obliterative changes in the vessels. In 1908, Posselt[11] discussed the use of the electrocardiogram and

TABLE 1.—*Symptomatology in Ten Cases*

Name, age and sex	First symptom	Presenting complaint	Shortness of breath	Cyanosis	Syncope	Cough	Hemoptysis	Chest pain	Orthopnea	Other
RR, 13, M	Cyanosis	Hemoptysis?	Ex. SOB when first able to walk, squatted to get breath	At 18 mo.	None	Upper respiratory infection	Gross, at 12 yrs.	None	None	Was known to have heart murmur as infant; can walk a block and a half at present
JS, 17, F	Ex. SOB, weakness gradual	Hemoptysis	Became SOB after sl. exertion for 4 yrs.; marked for 8 mo. before death	Terminally, at 17 yrs.	At 14 yrs.	At 14 yrs.	Gross at 14 yrs.; several times	None	None	Expired after minor operative procedure at 17 yrs.
BJ, 20, F	Ex. SOB	SOB	Gradual onset after delivery of child	At 19 yrs. Intermittent	Only weak spells	At 19 yrs.	Streaks, at 19 yrs.	Much, at 19 yrs.	19 yrs.	Gradually decompensated after delivery of child 2 yrs. before death; rt. heart failure
SW, 24, F	Ex. SOB	SOB; ? fainting	Ex. SOB, rather sudden onset at 20 years	None	At 20 yrs.	At 20 yrs.	None	At 24 yrs.	None	Still living; many syncopal spells associated with SOB; has had dependent edema.
JS, 30, F	Ex. SOB, paroxysmal tachycardia	Tachycardia	Ex. SOB began with 2nd pregnancy at age 25	At 30 yrs.	At 30 yrs.	Occas.	Streaks, at 29 yrs.	At 30 yrs.	None	Known murmur at 2½ yrs.; onset of symptoms with 2nd pregnancy; dyspnea & syncope outstanding features; pt. still living
RG, 34, F	Cough, fatigue	Cough	First noted Ex. SOB a few days before admission	At 34 yrs., Terminally	None	At 34 yrs.	Streaks, at 34 yrs.	None	None	Pt. died May 1951; cough and fatigue outstanding features; cyanosis terminally
PJ, 8, F	Asymptomatic	None	No	None	None	None	None	None	None	Murmur first noted at 3 months; patient has gotten along well
GF, 29, F	Hemoptysis	SOB	Ex. SOB is chief complaint since 27	None	None	Occas. nonprod. at 27 yrs.	Streaks at 26, gross at 27 yrs.	None	At 29 yrs.	Still living; gravida IX, para V, aborta IV
AG, 29, M	Ex. SOB	Chest pain	Ex. SOB age 28	None	At 29 yrs. with effort	None	None	Substernal & left arm, exertional	None	Died after minor surgical procedure
PH, 36, M	Ex. SOB	SOB	Ex. SOB	None	None	At 35 yrs.	None	Left chest	None	Still living but in chronic right heart failure

Ex. SOB—Exertional shortness of breath

t e teleroentgenogram in the diagnosis of p ulmonary hypertension. Sanders,[10] in 1904, r viewed the autopsy material in 7 cases and f und thickened intimal changes in the pul- r onary arterial segment along with right-sided h art failure. Monckeberg,[12] in 1907, presented v hat may be the first authenticated case of p imary pulmonary arteriosclerosis with clini- c l and microscopic confirmation. Moschco- v itz,[3] in 1927, believed that all sclerosis of the p ulmonary vascular tree was secondary to p ulmonary hypertension of various causes. I renner,[2] in 1935, clarified the concept of primary pulmonary arteriosclerosis. He defined the disease as "a rare condition in which there is sclerosis of the pulmonary arteries for no obvious reason (such as cardiac or pulmonary disease) as well as hypertrophy of the right but not of the left side of the heart." He made the statement that primary pulmonary arteriosclerosis is not one pathologic entity, but several different conditions with certain clinical and pathologic characteristics. Brenner thought that most of the cases in the literature were not adequately documented or that some other reason existed to account for the clinical and pathologic findings.

Brenner believed that the disease could be diagnosed clinically. He said that the symptoms were chiefly those of right ventricular failure, for which no adequate cause could be found. He was impressed with the minimal dyspnea and the absence of orthopnea in patients with intense cyanosis. In the cases that he reviewed, syncope, hemoptysis, and chest pain were uncommon. Edema, sometimes associated with ascites and pleural effusion, was a prominent symptom in most cases. He said that it is possible to diagnose the condition by the following points: (1) severe cyanosis and edema with comparatively little dyspnea; (2) clinical and electrocardiographic evidence of hypertrophy of the right ventricle but not of the left; (3) an accentuated pulmonary second sound, perhaps with a pulmonary diastolic murmur, without murmurs indicative of valvular or congenital cardiac disease; (4) clinical roentgenographic evidence of enlargement of the right heart with prominence of the pulmonary artery and conus of the right ventricle, but with a normal shadow of the left atrium; and (6) no evidence of syphilis.

Brill and Krygier[13] described the pathology as consisting of intimal proliferation in the pulmonary arterioles resulting in marked narrowing or occlusion of the lumen in many of the vessels and some recanalization. The larger and medium-sized arteries revealed little or no change from normal. There was associated right ventricular hypertrophy and no evidence of valvular damage or left atrial hypertrophy. Cross and Kobayashi[14] found similar pathologic changes with marked hyperplasia of the intimal endothelium in the arterioles, venules, and small veins. These changes were seen with right ventricular hypertrophy and right-sided cardiac failure.

Dresdale and co-workers,[15] in 1954, described the characteristic lesion as occurring predominantly proximal to the capillaries, which is consistent with our physiologic findings of a normal pulmonary capillary pressure in 3 patients.

Parmley and Jones[16] divided the clinical picture into 2 phases, respiratory insufficiency and cardiac insufficiency. The respiratory phase is predominantly characterized by dyspnea. In the second phase, the patient may develop venous distention, progressive peripheral edema, passive congestion, and effusions in the pleural, peritoneal, and pericardial cavities. They believed that syncopal attacks were rare and could be ascribed to cerebral hypoxia.

Review of Present Series of Patients

In our series exertional shortness of breath was present in every case and is probably the most distressing symptom that these patients have (table 1). Dyspnea at rest is a late symptom. More importance must be attributed to this symptom than in most other types of pulmonary congestion. Only 1 of our patients had had orthopnea. Six of our patients have had at least 1 episode of hemoptysis; 3 of them on more than 1 occasion. Six patients have been cyanotic, though none severely so. One patient was cyanotic shortly before death. Cyanosis was noted by the parents of 1 of these patients at 18 months of age and another at 3 years of age. They are now 13 years and 18 years old, respectively. Four of our patients complained of syncope related to exertion, and 1 patient had numerous "weak spells" with exertion but no loss of consciousness. Coughing was noted in all but 1 of our cases. It varied in severity,

TABLE 2.—*Physical Findings in Ten Cases*

Name, age, sex	Blood pressure	Pulse	Respiratory rate	Lungs and thorax	Chamber overactivity	Heart size	Thrill	Rhythm	A_2/P_2	Murmurs	Cyanosis	Clubbing	Abdomen	Habitus
RR, 13, M	120/97	80	20	Left chest straight, upper manub dullness; lungs clear	Both	AAL, retrosternal	Parasternal Gr. 3–4 syst.	SR	$P_2 > A_2$	Gr. 3 systolic pulmonary	Tips	None	Negative	Asthenic
JS, 17, F	140/100	112	20	Clear	Right	AAL, RSB 1+	None	Gallop	Not known	Gr. 2 pulm. syst. disappeared in upright position	Terminal only	None	Liver down 2 cm., tender	Sthenic
BJ, 20, F	102/84	100	38, moderate distress	Clear; left chest prominent	Right	AAL, retrosternal	LSB Gr. 3–4 diast.	SR	$P_2 > A_2$	Gr. 4 syst. mit., Gr. 1 mit. presyst.	Marked in nails	None	Liver down 2 FB tender	Asthenic
SW, 24, F	100/74	70	20	Moist rales right base posteriorly	Right	Enlarged to L & R: 1+ AAL 2–3+ RSB	None	SR	$P_2 > A_2$	Gr. 2 diast. pulm., Gr. 2 syst. mit.	None	Nonr	Liver down 1 FB, nontender	Asthenic
JS, 30, F	120/88	86	22, no distress	Clear	Right, marked	AAL RB retrosternal	None	SR	$P_2 > A_2$	Gr. 3 syst.	None	None	Negative	
RG, 34, F	100/70	116	32, marked distress with coughing	Dull both bases; decreased fremitus, bilat. moist rales, decreased breath sounds left base	Right	AAL 1+ RSB 2+	None	SR	$P_2 > A_2$	None	Present lips and nails	None	Liver down 3 cm., tender	Asthenic
PJ, 8, F	88/60	86	20, no distress	Clear	Right, marked; left, slight	AAL retrosternal	None	SR	Not known	Gr. 3 pulm. syst., Gr. 1–2 mitral systolic	None	None	Liver down 1 FB	Asthenic
GF, 29, F (Negro)	104/58	100–130	No distress	Clear	Right	MCL 2+ RSB 2+	None	SR, occ. gallop	$A_2 = P_2$	Pulm. syst., gr. 2 pulm. diast.	None	Not known	Liver down 3 FB, tender	Asthenic
AF, 29, M (Negro)	132/82	84	22, no distress	Clear	Right	MCL 1+ RSB 2+	None	SR, occ. gallop	$P_2 > A_2$	None	Terminal only	None	Negative	Sthenic
PH, 36, M	120/80	96	20	Clear	Right	AAL	None	SR	$P_2 > A_2$	Gr 3 mit. syst., Gr. 2 mit. presystolic	During marked exercise	None	Liver down 3 FB	Sthenic

AAL—anterior axillary line, FB—fingerbreadths, RSB—right sternal border, MCL—midclavicular line, SR—sinus rhythm

TABLE 3.—*Laboratory Findings in Ten Cases*

Name	X-Ray	ECG	HGB	RBC	WBC	Urine	Miscellaneous
I R	RVH; prominent pulmonary vascular markings	RVH	14.0	4.9	7.4	Normal	
J S	Normal	Normal	12.5	4.7	6.8	Normal	
I J	RVH; marked pulmonary arterial enlargement	RVH	17.8	4.5	7.7	25–30 RBC; 2–3 finely granular casts	VC 74%; VP 12.2 cm. H_2O; CT 35 sec. (Decholin); VC 2.2 L 67%
S W	RVH; prominent pulmonary arterial segments	RVH	Not done	Not done	Not done	Normal	
J S	RVH; prominent pulmonary arteries; prominent vascular markings increased throughout lung field	RVH	14.8	4.61	7.0	Normal	VP 30 cm. H_2O; CT 22 sec. (Decholin)
R G	RVH; prominent pulmonary arterial segments; unusual increase in vascularity in all lung fields	RVH	14.3	4.6	11.3	Normal	
P J	RVH; prominent pulmonary arterial segments	RVH	11.8	4.02	9.6	1.033, alk.; Neg.; Occas. RBC	
G F	RVH; prominent pulmonary vascular markings	RVH	13.0	3.6	12.1	3–4 RBC/HPF	
A G	RVH; prominent pulmonary vascular markings	RVH	16.0	6.28	9.65	1.018	VC 2400 ml.; VP 9.8 cm. H_2O; A to T CT 11 (Decholin) A to L CT 12 (Ether)
P H	RVH; prominent pulmonary vascular markings	RVH & postmyocardial ischemia	14.5	5.1	8.6	Not done	CT A to L 10; CT A to T 20

RVH—Right ventricular hypertrophy; VC—Vital capacity; VP—Venous pressure; CT—circulation time; A to L—arm to lung; A to T—arm to tongue.

however, from an occasional dry cough to severe episodic bouts productive of frothy, purulent, or bloody sputum. Chest pain was present in 4 of our patients and was severe in 2 of them. Chest pain was predominantly substernal in character, and, in some, with radiation down both arms on exertion. The pain was at times relieved by nitroglycerin. In some, "catching" chest pain with respiration between these episodes was present. The substernal pain may in part be due to pulmonary hypertension and also to coronary insufficiency.

All except 2 of our patients were slender and undernourished (table 2). Systemic hypertension was not present in any of them. Three were cyanotic when first seen, and 3 others were cyanotic shortly before death. Minimal clubbing of the fingers was present in 1 patient. The lungs were usually clear to physical examination, though bilateral crepitant rales were noted in 1 case, and evidence of pleural effusion in 1 case. Right ventricular overactivity was present in all cases. The heart was enlarged to the left of the midclavicular line by percussion in all but 1 case and to the right of the sternum in 5. Thrills were palpable along the left sternal border in the third and fourth interspaces in 2 patients. All of our patients had a regular sinus rhythm with a pulse rate of between 70 and 130/min. P_2 was loud and greater than A_2 in all except 1 case. Eight of our 10 patients had murmurs. These were predominantly pulmonary systolic murmurs, though pulmonary diastolic murmurs were noted in 2 instances. Two patients had an apical systolic murmur, and 2 patients had a questionable apical presystolic murmur. In 6 cases the liver was moderately enlarged and tender.

Teleroentgenograms and fluoroscopy revealed right ventricular hypertrophy, prominent pulmonary arterial segments, and frequently dilated pulmonary trees well out into the lung parenchyma (table 3). In some, marked pulsations were seen in the pulmonary hilar vessels. In addition, uniform lack of parenchymal lesions and failure of the left

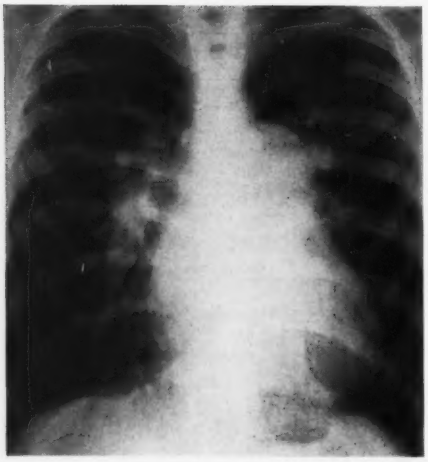

FIG. 1. Posteroanterior teleroentgenogram revealing right ventricular hypertrophy and prominent pulmonary arterial segments.

atrium to show enlargement helped complete the picture (fig. 1).

The electrocardiographic tracings indicated right ventricular hypertrophy in 9 of 10 cases. In 2 of the far-advanced cases ischemic T wave changes were also noted. No excessive P wave changes were noted (fig. 2).

One of the autopsied cases revealed right ventricular hypertrophy with a normal electrocardiogram.

Routine laboratory procedures were of little diagnostic importance in our cases. An elevated erythrocyte count and hemoglobin were found in 2 of our patients. The serologic tests for syphilis were negative in all cases.

REVIEW OF CARDIAC CATHETERIZATION DATA IN OTHER CASES

Dresdale's group[15] catheterized 3 patients, and all revealed greatly increased pulmonary, right ventricular, and right atrial pressures. In the 1 patient in whom the pulmonary capillary pressure was obtained, it was found to be normal. In all 3, the resting arterial oxygen saturations were normal, and it was only slightly decreased in 1 patient after exercise.

Soothill[17] reported a cardiac catheterization of a 22-year-old woman with greatly elevated pressures in the right atrium (26/12 mm. Hg), right ventricle (54/17 mm. Hg), and pulmonary artery (128/83 mm. Hg), and a decreased cardiac output of 1.3 L./M.²/min.

TABLE 4.—*Cardiac Catheterization Findings Pressures (mm. Hg)*

Patient*	Right atrium	Right ventricle	Main pulmonary artery‡	Pulmonary capillary pressure	Cardiac index L./min./M.²
RR	3/−1	130/30	110/70		
JS	2/−2	87/6	80/40		
BJ	10/0	60/0	60/39		
SW	5/2	100/5	98/78 (88)		
JS		75/15	65/35		
RG†					
PJ	5/1	95/25	97/75 (82)		
GF	5/2	100/5	98/78 (88)	12	
AG	10/3	155/5	160/90 (115)	11	Resting cardiac index 2.01
PH	5/2	85/10	85/25	14	Resting cardiac index 1.8; Exercise cardiac index 1.7

* Oxygen levels were within normal limits on all these patients, with no evidence of left-to-right shunt.

† Angiography revealed right ventricular hypertrophy, prominent pulmonary vascular tree, and no evidence of shunt. Catheterization not done.

‡ Figures in parentheses are mean pressures.

TABLE 5.—*Necropsy Findings*

Name, age, and sex	
AG 29 F	Right ventricular hypertrophy; pulmonary arteriolosclerosis; small atherotic plaque, pulmonary artery; valve areas normal and no left atrial enlargement; pleural effusion, bilaterally
RG 34 F	Right ventricular hypertrophy; pulmonary arteriolosclerosis; bilateral pleural effusion and ascites, peripheral edema; valve areas normal
BJ 20 F	Right ventricular hypertrophy; pulmonary arteriolosclerosis; pulmonary arteriosclerosis with one plaque; peripheral edema; valve areas normal
JS 17 F	Right ventricular hypertrophy; pulmonary arteriolosclerosis; normal valve areas; small peripheral pulmonary infarction; small area of bronchopneumonia

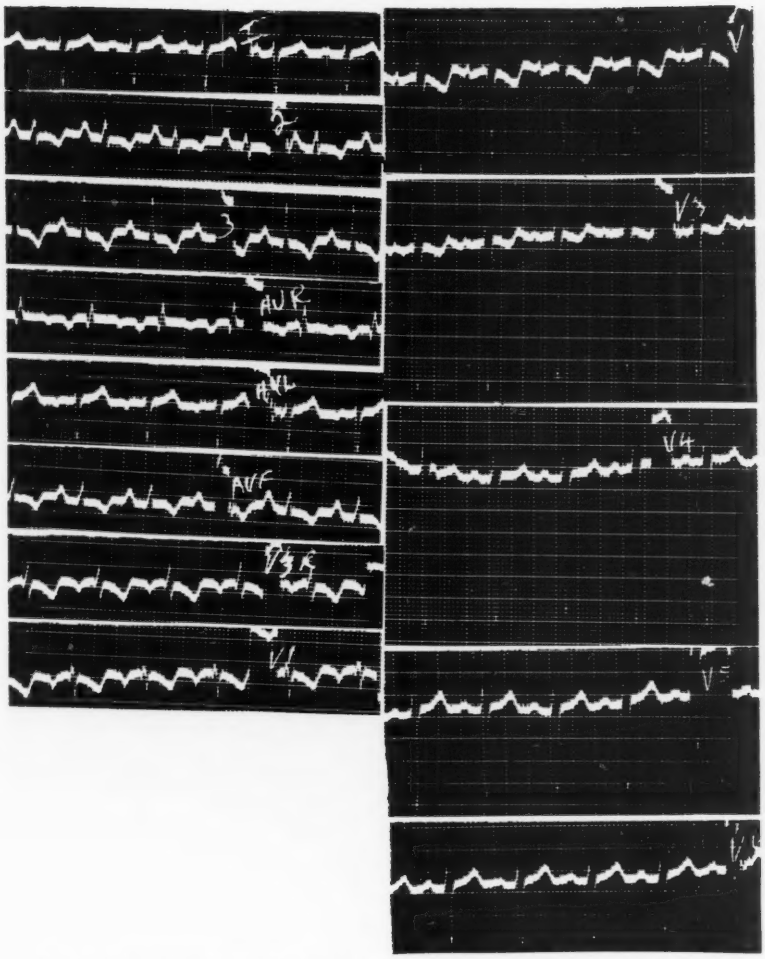

FIG. 2. Electrocardiographic tracing revealing right ventricular hypertrophy

Dressler[18] stressed the diagnostic importance of high pulmonary arterial pressures in the disease and no change in the arterial oxygen saturation with exercise.

Dexter[19] reported 4 cases in which venous catheterization of the heart was performed. The cardiac index was reduced in 3 and the stroke output was reduced in all 4. The arterial oxygen saturations were 77, 89, 94, and 93 per cent. The pulmonary arterial pressures were reported as 110/50 mm., 110/60, and 80/65 Hg, and the right ventricular pressures were elevated in patients with failure. The pulmonary capillary pressures were reported as 10 in the 2 instances in which it was done. The total pulmonary resistance and pulmonary vascular resistance were markedly increased.

In all of our 9 patients that were catheterized, high right ventricular and pulmonary arterial pressures were uniformly found (table 4). The 3 pulmonary capillary pressures that were obtained were within normal limits. This may be a very important diagnostic point in the differentiation from secondary pulmonary hypertension in which the so-called "wedge pressure" is frequently elevated. This suggests a high resistance in the pulmonary arterioles prior to the pulmonary capillary

FIG. 3. Heart and lungs, revealing marked right ventricular hypertrophy, small yellow atheromatous plaques in main pulmonary artery, and 2 small hemorrhagic infarcts in the lungs.

area. Cardiac outputs were reduced in the 2 patients in whom they were obtained.

Cross and Kobayashi[14] reported that a 20-month-old infant who received 75 ml. of saline and 25 ml. of plasma suddenly became cyanotic, collapsed, and died almost instantaneously. In 1 patient in whom all the catheterization procedures had been successfully completed, a final 25 ml. of Diodrast was injected into the pulmonary artery; the patient almost immediately developed a convulsive seizure, became cyanotic, and died. These experiences emphasize the relative rigidity of the pulmonary vascular tree and the possible high degree of "precapillary block" in such patients, and suggest the need for extreme caution in carrying out catheterizations. Unless the case is quite unusual, we believe that catheterization should not be performed.

Dresdale and co-workers[15] noted that the ventilatory capacity was reduced at rest, and the rise with exercise was less than expected. In 2 of our patients with extensive pulmonary function studies, the only abnormality noted was a slight diminution in the timed vital capacity.

The most characteristic findings of primary pulmonary arteriosclerosis were those in the lung microscopically and in the heart grossly. The heart was enlarged as a result of right ventricular hypertrophy (fig. 3). The right ventricle measured up to 4 times its normal thickness, while the left ventricle was either normal or less than normal. The right ventricle varied in thickness from 10 to 30 mm., having a homogeneous red-brown appearance. Areas of focal fibrosis were seen grossly. The endocardial surfaces were smooth and glistening, and the valves showed no deformities. There was little coronary or generalized arteriosclerosis. This latter finding, however, depended to a great degree upon the age of the

FIG. 4. Lung. Note marked endothelial and subendothelial proliferation of cells. There is some thickening of the media and adventitia. The size of the lumen is markedly reduced. × 200.

patient, but characteristically no arteriosclerosis was present within the coronary system. In all 4 of our patients, the pulmonary artery was larger in total circumference than the combined circumference of the pulmonary veins. This is the reverse of the normal findings.

The gross examination of the lungs revealed little pathologic change. These patients were more susceptible to infectious diseases, and at the time of autopsy areas of bronchopneumonia were discernible in 1 of the patients. One case here reported showed multiple small infarcts, which several other authors have reported as a frequent finding. The infarcts appeared as wedge-shaped airless portions of lung located in the periphery, and were quite small.

Microscopically, the only observations of significance were in the lungs. The lumina of the middle-sized and smaller pulmonary arteries and arterioles were strikingly reduced in size (fig. 4). The capillaries showed no changes. Occasionally, soft, small, yellow, raised atheromatous plaques were found in the major pulmonary arteries; they were noted in 2 of our patients. In the middle-sized and smaller arteries and arterioles, there was a marked increase in the depth of subendothelial space due to numerous lipoid-laden mesothelial cells. Occasionally, cholesterol clefts were present, but calcification was not prominent. This fatty material stained positively with Sudan III. The intima was usually intact but frequently the lumina of these small vessels have been completely obliterated by organized thrombi and subintimal fibrosis.

In some areas, there was evidence of recanalization. Fresh thrombi were not observed in this study. A notable finding was the distinct thickness of the musculature of the smaller arteries and arterioles, which by differential staining technics proved to be an increase in fibrous connective tissue without increase in muscular component. The elastic lamina were usually quite prominent and appeared to be intact by special elastic stains.

In 1 patient, areas of organizing pneumonia and areas of thickened alveolar septa due to old inflammatory reaction were seen. Emphysema was also frequently observed.

Microscopically, the myocardium of the right ventricle showed only evidence of hypertrophy with large "boxcar"-shaped nuclei and large muscle bundles. Frequently, the myocardium showed evidence of focal myocardial fibrosis.

Our 4 necropsied cases all showed evidence of right ventricular hypertrophy. There was marked hypertrophy of the intima in the pulmonary arterioles. In 2 there were atherosclerotic plaques in the pulmonary artery. In 1 there was a questionable malformation of the arterioles and capillaries. The pulmonary parenchyma was normal, and the left atria were normal in all cases. In 1 case multiple small peripheral infarctions were seen.

Differential Diagnosis

Eisenmenger's complex can be differentiated with exercise, according to Dexter,[19] because of the much greater increase in pulmonary arterial pressure in primary pulmonary hypertension. He further believed that the pulmonary capillary pressure would be normal, despite the elevated pulmonary arterial pressure, and found it so in 3 of the 4 cases he catheterized. Capillary pressures may also be normal in Eisenmenger's complex. Right ventricular oxygen step-up, angiocardiograms, and dye-dilution curves aid in making this differentiation.

Interatrial septal defects reveal evidence of a left-to-right shunt on cardiac catheterization and, in some, it may be possible to direct the catheter tip through the septal defect into the left atrium. Electrocardiographic tracings usually show conduction disturbances, most commonly right bundle-branch block or atrioventricular blocks, unlike primary pulmonary hypertension, which shows only right ventricular hypertrophy, with or without ischemic T wave changes.

Mitral stenosis may present a history of previous active rheumatic fever. The P waves on the electrocardiographic tracings are frequently broadened and notched and right bundle-branch block is frequently seen. The teleroentgenogram in the right anterior oblique position usually reveals left atrial hypertrophy. An opening snap or presystolic localized apical murmur helps differentiate the condition, although rarely the presystolic component may occur in association with primary pulmonary hypertension. Congenital mitral stenosis does not always show left atrial enlargement by fluoroscopic examination, and without pulmonary "wedge" pressures may be confused with primary pulmonary hypertension. Endocardial fibroelastosis occasionally must be considered in the pediatric age group, but the electrocardiogram aids in the differentiation. In endocardial fibroelastosis there is usually subendocardial injury and left ventricular hypertrophy. Cor triatriatum must be ruled out by the same method as congenital mitral stenosis, since they cannot be separated clinically.

Pulmonary stenosis with its loud systolic murmur and its diminished or absent second pulmonary second sound must also be ruled out. The post-stenotic dilatation of the pulmonary artery, frequently seen on the left with relatively clear lung fields, combined with high right ventricular pressure and normal or low pulmonary arterial pressure helps to establish its identity.

Because of the syncope Dressler[18] emphasized the necessity of ruling out neurosis and hysteria. He believed the mechanism of syncope may be due to decreased cerebral blood flow secondary to decreased cardiac output or to vasovagal reflex. Dressler stressed the importance of effort syncope as an early manifestation of primary pulmonary arteriosclerosis.

He suggested that it is due to a reflex mechanism originating in neuroceptors in the wall of the pulmonary artery, using the vagus nerve as an afferent pathway, and resulting in a fall of the systemic blood pressure and inhibition of the heart beat. Syncope is usually not encountered with mitral stenosis, the congenital heart diseases with which primary pulmonary hypertension might be confused, or chronic cor pulmonale. The syncope of primary pulmonary hypertension must be differentiated from supraventricular or ventricular arrhythmias, carotid sinus and vasovagal syncope, acute left ventricular failure, as seen with advanced aortic stenosis or myocardial infarction, ball-valve thrombi, and venoarterial shunts.

Course and Prognosis

Of the original 10 cases followed by us, 4 have already died: 2 who died during minor surgical procedures showed intermittent or no cyanosis, and 2 who died in right-sided cardiac failure showed terminal cyanosis. Of the 6 surviving patients, 5 had exertional dyspnea, 3 had chronic right heart failure, 3 had cyanosis, and 2 had syncope. There was only 1 patient, aged 8 years, who was relatively asymptomatic. The course, although variable in duration, was ultimately that of fairly intractable and progressive failure of the right ventricle with maintenance of a sinus rhythm and a lack of orthopnea. From the onset of symptomatology to the termination of the disease, De Navasquez[20] observed that the course varied from 5 months to 5 years. This may usually be true, but we have seen 1 patient with symptoms of exertional shortness of breath for 12 years who is still getting along fairly well without right heart failure.

Chess and Yonkman,[21] noted that tolazoline hydrochloride (Priscoline), possibly through its adrenolytic and sympatholytic actions, reduced the pulmonary arterial pressure and increased pulmonary blood flow. The parenteral effects of Priscoline are of short duration, up to 20 to 30 min., and the response to chronic oral administration of the drug was inconclusive. This observation suggested sympathectomy as a therapeutic approach to the problem. However, extensive stripping of the sympathetic nerve supply to the pulmonary vascular tree has been very disappointing.[22] In 2 patients in whom we used oral Priscoline, no apparent symptomatic improvement was noted. Because of the occasional tendency to spontaneous pulmonary thrombosis, anticoagulant therapy might be considered, but it has not been used as yet to our knowledge.

Summary

A brief historical review of primary pulmonary arteriosclerosis and hypertension has been given. Ten additional cases with detailed laboratory, roentgenographic, electrocardiographic, cardiac catheterization, and angiocardiographic studies are presented. The findings on 4 necropsied cases are also included. Progressive exertional shortness of breath, syncope, and left chest pain with roentgenographic and electrocardiographic evidence of right ventricular hypertrophy, pulmonary arterial dilatation, high right ventricular and pulmonary arterial pressure, and normal pulmonary capillary pressure in the absence of pulmonary disease should be extremely suggestive of primary pulmonary hypertension. An unrelenting downhill course of right ventricular failure is usually seen.

Summario in Interlingua

Es presentate un breve revista historic de primari arteriosclerosis e hypertension pulmonar. Es addite dece nove casos con detaliate studios laboratorial, roentgenographic, electrocardiographic, de catheterisation cardiac, e angiocardiographic. Es etiam includite le constatationes de 4 necropsias. Progressive dyspnea post effortio, syncope, e dolores sinistrothoracic con evidentia roentgenographic e electrocardiographic de hypertrophia dextero-ventricular, dilatation pulmono-arterial, alte pression dextero-ventricular e pulmono-arterial, e normal pression pulmono-capillari in le absentia de morbo pulmonar deberea esser prendite como un forte indication de hypertension pulmonar. Un persistente deterioration del disfallimento dextero-ventricular es usualmente a notar.

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One must be a professional Ulysses in craft and wisdom not sometimes to err in estimating the nature of an attack of severe heart pain. There is no group of cases so calculated to keep one in condition of wholesome humility.—WILLIAM OSLER. *Angina Pectoris and Allied States*, 1897.

Comparison in Man of Adrenergic Blockade Produced by Dibenzyline, Ilidar, Priscoline, and Regitine

By HAROLD D. GREEN, M.D.

A method is presented for analyzing the probable effectiveness of blocking drugs in relieving vasospasm in the extremities, and comparison is given of the relative potency and side effects of 4 adrenergic blocking drugs and of their effects on heart rate, arterial pressure, and cardiac output, as estimated from a "circulatory index." Data are also given on the use of these drugs in evaluation of the circulation in patients.

IN EVALUATING the status of the peripheral circulation in man, it is necessary to differentiate between the impairment of blood flow due to organic obstructive disease and that due to excessive vasospasm. This differentiation can be accomplished by determining the maximal peripheral flow after relaxation of all vasospasm. Drugs capable of relaxing vasospasm are also potentially useful in the therapy of vasospastic conditions. In a similar previous study it was shown that tolazoline hydrochloride (Priscoline hydrochloride) and phentolamine methanesulfonate (Regitine) were effective vasodilators but that beta-pyridyl carbinol (Roniacol) was practically ineffective.[1] In this paper we compare the effectiveness of 2 new drugs, azapetine phosphate (Ilidar phosphate) and phenoxybenzamine hydrochloride (Dibenzyline), and a tolazoline-phentolamine combination with that of tolazoline alone used as a reference standard.

METHODS

Peripheral circulation was evaluated by placing subjects in a constant temperature room under controlled conditions and recording temperatures of the skin of 2 fingers on each hand, 3 toes on each foot, and the forehead with a 12-point Brown potentiometer. Copper-constantin thermocouples were held in contact with the skin by means of cellophane strips placed 1 cm. from the thermocouple tip. The wires were curved in such a way that the tip was held firmly against the skin without being covered at the tip by the cellophane. The recorder required 2½ min. to complete each cycle of 12 readings. Blood flow and vasoconstriction were estimated from the relationship of the temperatures of the skin to room and forehead temperatures. Minimal blood flow, due to maximal vasoconstriction, was considered to exist when the skin temperatures approximated room temperature, and maximal blood flow, due to maximal vasodilatation, when the skin temperatures approximated the forehead temperature. Approximately a 15 C. differential existed between room and forehead temperatures.

The studies, conducted on 10 volunteer normal medical students, were carried out in a room in which the temperature was maintained at 19.5 to 20.5 C. The air in this room circulated at a velocity of approximately 120 feet/min. and varied in humidity between 44 and 72 per cent of saturation (average: for summer, 66; for winter, 48). Exposure to this environment, while clad only in shorts, induced strong vasoconstriction in all the subjects as indicated by the progressive decline of the temperatures of the fingers and toes to 19 to 24 C. during the 45 to 90 min. of initial cooling prior to administration of the drug. The subjects were maintained in the same environment and degree of exposure throughout the study; no warming was applied to any part of the body.

The 4 adrenergic blocking agents used to induce vasodilatation in this study were tolazoline hydrochloride, used for comparison with the previously reported studies,[1] and azapetine phosphate, phenoxybenzamine, and a tolazoline-phentolamine combination. The structural formulae of these drugs have been presented elsewhere.[2]

Each drug was diluted in 200 ml. of 0.9 per cent saline and administered intravenously over a period of 30 to 45 min., zero time on the chart being the beginning of the drug administration. The 10 subjects received each of the 4 drugs in turn on separate days. No vasodilator drug was administered until maximal vasoconstriction was induced. During administration of the drugs the blood pressure and pulse rate were recorded at least every 5 min.

Before the drugs were used for these studies, ex-

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periments were performed on dogs to evaluate the dose needed to produce any toxic effects. The minimal toxic dose was divided by 10 and used as the starting dose for this study. In the preliminary studies on the students the dose was increased cautiously until a desired effect was obtained or until toxic effects were produced. The dose used in these studies was considered to be either an effective dose or the maximum safe dose to be used by this method of administration.

Results

Tolazoline (*Priscoline*). Tolazoline was given to each subject in a dose of 2 mg./Kg. of body weight. The results obtained with this drug were comparable to those reported previously when body warming was not used.[1] Figure 1 shows the temperature responses in 1 finger and 1 toe of each of the 10 subjects. In the fingers, an excellent response occurred in 3, a fairly good response in 6, and a poor response in 1 subject. In the toes, excellent responses occurred in all but 3 subjects. The mean maximal responses are given in table 1*A* and *C*.

The average heart rate increased 12 per cent (table 1*G*), which was significant at the 5 per cent level. The incidence of changes of arterial pressure is summarized in table 2.

During the administration of this drug, shivering sensations, rather severe flushing of the skin of the face, neck, and back, and redness of the eyes were noted (table 3). The flushing of the skin disappeared within 1 hour after completion of the drug administration and the redness of the eyes within 2 to 3 hours. The shivering stopped upon cessation of the drug administration. With the completion of the studies, all subjects were able to arise and to continue their work or studies with no discomfort.

Azapetine (*Ilidar*). Each subject received 1 mg./Kg. of this drug. The temperature responses of the fingers were significantly better than, and those of the toes slightly less than, those noted with tolazoline (fig. 1 and table 1*A* and *C*).

No sudden or immediate drop in the arterial blood pressure occurred while the drug was being administered. In a small number of the subjects there was a gradual decline in arterial pressure; in others it remained stable (table 2). The heart rate increased slightly but not significantly (table 1*G*).

Nasal congestion was noted during the drug

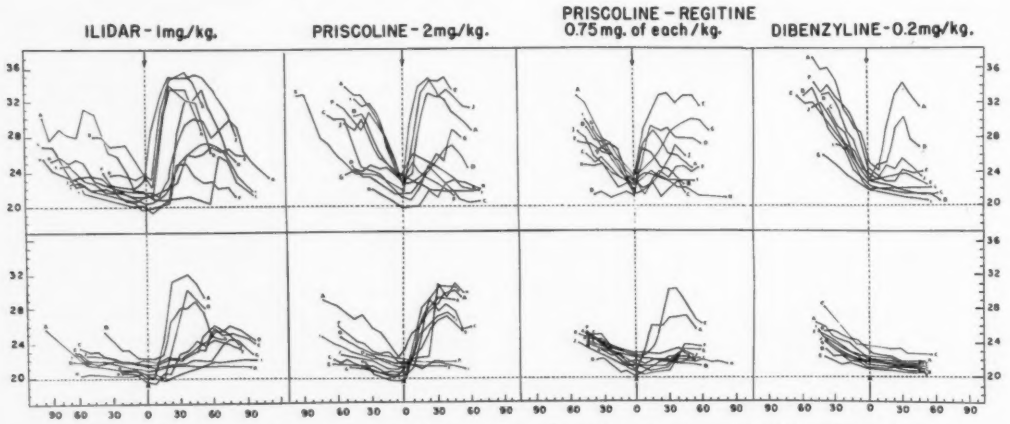

Fig. 1. Skin temperature responses (degrees C., ordinate), in the tips of the index finger (upper graphs) and of the large toe (lower graphs) in normal man, to intravenous infusion of various blocking drugs. The 4 drugs studied and their doses are given in the headings. The same 10 subjects were used successively on separate days for each of the 4 drugs. Each study was performed at a room temperature of 20 C. ± 0.5 C. In order to induce a maintained state of vasospasm, each subject was exposed to this temperature for 45 to 90 min. prior to and throughout the study while clad only in shorts. The subjects were all fasting and had not exercised prior to the drug infusion, which was begun at 0 time (abscissa) and continued for 30 to 45 min. The drugs are arranged in the order of relative clinical efficacy based upon response vs. side effects. Ordinate, skin temperature in degrees C.

TABLE 1.—*Mean and Variability of Responses in Ten Normal Medical Students*

			Mean. standard error,† probability	Azapetine	Tolazoline	Tolazoline-phentolamine	Phenoxy-benzamine
Maximal skin temperatures (C.)	Index finger	A	Mean	30.8	28.2	26.9	24.8
		B	S.e.	1.3	1.5	1.0	1.3
			p‡	0.017	—	0.18	0.003
	Great toe	C	Mean	26.1	27.0	23.9	20.9
		D	S.e.	1.7	1.2	0.9	0.2
			p‡	0.41	—	0.0001	0.0001
Heart rate	Control	E	Mean	67.2	64.6	66.0	66.8
		F	S.e.	1.6	3.2	2.2	3.7
	Exp. per cent of control	G	Mean	105.9	112.2	106.3	99.6
		H	S.e.	10.4	4.9	2.6	2.9
		I	p§	0.55	0.035	0.035	0.94
Control arterial pressure	Systolic	J	Mean	112.9	112.9	114.5	115.4
		K	S.e.	2.0	2.7	1.9	2.4
	Diastolic	L	Mean	70.5	69.9	68.8	70.8
		M	S.e.	2.7	1.7	2.2	2.6
Corrected pulse pressure*	Control	N	Mean	63.7	63.6	67.8	65.2
		O	S.e.	3.0	2.7	2.2	4.7
	Exp. per cent of control	P	Mean	113.0	114.1	106.6	106.2
		Q	S.e.	5.4	5.4	6.6	5.6
		R	p§	0.04	0.0255	0.35	0.30
Circulatory index (H.R. × corrected P.P.)	Control	S	Mean	4308	4129	4496	4476
		T	S.e.	280	333	259	55
	Exp. per cent of control	U	Mean	120.4	129.7	113.8	106.0
		V	S.e.	8.4	10.8	8.4	7.0
		W	p§	0.04	0.023	0.125	0.42

* Corrected pulse pressure was calculated as:

$$\textit{Corrected pulse pressure} = \frac{\textit{Measured pulse pressure} \times \textit{cycle length (seconds)}}{\textit{Diastolic length (seconds)}}.$$

The cycle length was computed from the heart rate, and the diastolic length from the data of Katz and Feil.[3]

† S.e. = Standard error of mean based on $N = 10$ observations in all cases.

‡ The likelihood that the difference between the indicated mean and the mean for tolazoline could occur by chance.

§ The likelihood that the difference between the indicated per cent of control and 100 per cent could occur by chance.

Both sets of probability values were read from a chart of t vs. probability, prepared by James F. Crow, which may be obtained from the Department of Zoology, Dartmouth College.

administration and for 1 to 2 hours following (table 3); drowsiness and slight vertigo persisted for about 24 hours and redness of the eyes for 1 to 2 hours.

Tolazoline-phentolamine (Priscoline-Regitine) Combination. Two subjects received 0.5 mg./Kg. of each drug and the other 8 received 0.75 mg./Kg. The temperature responses in the fingers were on the average less than those noted with tolazoline alone and were significantly less than those noted with azapetine. In the toes there was a significantly smaller response than that to either tolazoline or azapetine (fig. 1; table 1*A* and *C*).

Except for 2 subjects there was no change in arterial pressure (table 2). There was a small but significant increase in heart rate.

Phenoxybenzamine (Dibenzyline). Phenoxy-

TABLE 2.—*Incidence of Arterial Pressure Changes During Administration of Adrenergic Blocking Drugs*

	Systolic pressure		Diastolic pressure	
	Change mm. Hg	No. subjects	Change mm. Hg	No. subjects
Azapetine	−10	3	−5	2
	−5	1	−8	1
Tolazoline	+5 to +10	5	0	
	−10	1		
Tolazoline-phentolamine	+10	1	+10	1
	−10	1	−10	1
Phenoxybenzamine	−10	1	0	
	−5	1		

TABLE 3.—*Side Effects Experienced*

Symptom	Number of subjects experiencing symptom			
	Azapetine	Tolazoline	Tolazoline phentolamine	Phenoxybenzamine
Nasal stuffiness	8		10	10
Redness of eyes	3	7		
Shivering		6		
Drowsiness	3			
Flushing of skin		7		
Vertigo	3			
Delayed shortness of breath and tiredness				3
Palpitation				1

benzamine was given to all subjects in a dose of 0.2 mg./Kg. There was no response in the toes of any subject, the temperatures continuing to drop slightly during the drug administration. In the fingers, there was a slight response in 3 and a good response in 2 (fig. 1); on the average, however, the responses were significantly poorer than were those to tolazoline or azapetine (table 1*A*).

The systolic arterial pressure dropped in 2 subjects (table 2). The pulse rate was unchanged by the drug.

Nasal stuffiness, noted during the drug administration, lasted 4 to 8 hours afterwards and was not relieved by nose drops. Upon completion of the studies, all students were able to get up and walk about with no untoward symptoms. Approximately ½ to 1 hour after the study, 3 of the subjects noted shortness of breath and tiredness after slight exertion and 1 noted a definite palpitation of the heart with rapid pulse; all 4 found it necessary to lie down for 1 to 2 hours.

Circulatory Index. To obtain a measure of the change in cardiac output we computed a "circulatory index," which, for this paper, is defined as the product of the heart rate and a corrected pulse pressure. It is based on the assumption that the stroke volume roughly parallels the corrected pulse pressure. The corrected pulse pressure was computed from the heart rate and recorded pulse pressure according to the simple equation given in the legend to table 1. In this equation it is assumed that the pressure drop during diastole is proportional to the diastolic "run off" and that, if all the blood were ejected during the first instant of systole, the systolic pressure would rise to some value higher than that recorded and that the pressure drop during the entire cycle would then be proportional to the "run off" during the whole cycle, which would in turn be proportional to the stroke volume. This circulatory index increased significantly with both azapetine and tolazoline.

DISCUSSION

Relatively speaking, all the drugs were pushed to a reasonably safe maximum level. Under these conditions the best responses were obtained with tolazoline and azapetine, which compared favorably in this series of studies. Both drugs increased the temperatures in the fingers and toes approximately equally in all subjects and both caused a minimum of discomfort accompanying and following the administration. The tolazoline-phentolamine (Priscoline-Regitine) combination, which has a smaller dosage of tolazoline than the tolazoline alone, was less effective in overcoming vasospasm and caused considerably more severe nasal stuffiness than either azapetine or tolazoline alone. In the dosage used, phenoxybenzamine was not effective in overcoming vasospasm in the lower extremities and only slightly effective in the fingers. The dosage was not increased because of the unpleasant side effects, particularly the delayed symptoms that suggested postural hypotension.

In general the subjects who responded well with tolazoline were likely to respond better with the other drugs, and those who responded poorly with tolazoline usually also did poorly with the other drugs. In a given subject a good response in the toes was usually accompanied by a good response in the fingers and, conversely, a poor response in the fingers was almost always accompanied by a poor response in the toes.

The data in table 1 suggest that, in the doses given, tachycardia was produced most consistently by tolazoline, +12 per cent, and by the tolazoline-phentolamine combination, +6 per cent; the other drugs caused little or no significant increase in heart rate. On the average, pulse pressure tended to be increased with all 4 drugs, but significant increases were seen only with tolazoline and azapetine. Cardiac output per minute, as estimated from the "circulatory index," was increased significantly only with azapetine and tolazoline.

In animals, phenoxybenzamine and phentolamine seemed to be 3 to 10 times as potent as tolazoline and azapetine in blocking adrenergic stimulation.[4-7] From the present studies it would appear that, in man, they are more nearly of equal potency, although phenoxybenzamine was not given in a dose large enough to produce effects comparable with those of the other drugs.

Moser and co-workers[8] studied the blockade of vasospasm induced by exposure to temperatures of 19 to 22 C. and found that they had to use 0.7 to 1.0 mg./Kg. of phenoxybenzamine. They noted that their subjects had to be kept flat for 2 to 3 hours after the test and had to be very careful for 24 to 48 hours afterwards to avoid postural hypotension. We deliberately used smaller doses in order to avoid such delayed symptoms. Doses of tolazoline, azapetine, tolazoline-phentolamine, and phentolamine alone,[1] which caused much better blockade, did not have this prolonged, delayed effect.

In the study mentioned above and in another by Ford and associates[9] rather large doses of phenoxybenzamine were used (in the latter a total dose of 95 mg. was given). These doses were sufficient to block the rise in arterial pressure that would normally follow an intravenous infusion of arterenol. Tests of adrenergic blockade *per se* were not carried out during our studies. A separate series of experiments suggests that the doses used in our study were sufficient to reverse the pressor response to 0.1 mg./Kg./min. of epinephrine but only reduced and did not abolish the pressor response when the same dose of arterenol was given intravenously. When we use the adrenergic blocking drugs in patients, we consider it important not to exceed the doses used in this study, since an occasional patient will show a considerable drop in arterial pressure with these doses. Moreover, it is important that the blockade be such that arterenol (Levophed) or phenylephrine (Neosynephrine) can be used by intravenous drip to restore and maintain the arterial pressure.

To date, 376 temperature studies have been made in patients, with the technic described in this paper for the drug administration plus body warming to enhance the dilator response:[1] one hundred and two were done with tolazoline, 80 with phentolamine alone, and 194 with azapetine. There have been no serious complications in any of these patients. Phenoxybenzamine has not been used for temperature studies in patients because of the relatively poorer response noted at doses tolerated reasonably well in the 10 normal subjects. The tolazoline-phentolamine combination also has not been used in patients because of the relatively poor response and the relatively high incidence of side effects in the 10 normal subjects. It was not possible to repeat the studies on the same patient with all 3 of these drugs. In order to estimate the relative effectiveness of 3 of these drugs in patients, we have com-

TABLE 4.—*Means of Maximum Temperatures Reached in Patients During Routine Studies, Body Warming Used in Addition to the Blocking Drug*

	No. of studies analyzed	Finger		Toe	
		Right	Left	Right	Left
A. Tolazoline	100	31.7	32.2	26.8	27.14
B. Phentolamine	79	32.8	32.9	27.0	28.3
C. Azapetine	194	32.4	32.76	28.53	28.28
D. Probability					
A vs. B		0.12	0.48	0.8	0.1
A vs. C		0.28	0.28	0.0003	0.08

pared the maximal skin temperatures reached in all of these patients for each of the 3 drugs. Such comparison is valid only to the extent that in a large enough series of patients the proportion of severe obliterative disease will be the same for each group. The results of this analysis are reproduced in table 4, which shows that in the doses used the 3 drugs were essentially equally effective, although azapetine may be slightly better than tolazoline in the toes.

Early signs of impending fall of arterial pressure are nausea, pallor, tachycardia, and weakening of the radial pulsations. Any of these symptoms is an indication for stopping the drug and the institution of restorative procedures. The incidence of such side effects has been carefully analyzed for the first 143 of the patients receiving azapetine. In all these patients the calculated dose was 1.0 mg./Kg. of body weight. In 40 of them the azapetine had to be stopped after administration of one fourth to four fifths of the calculated dose because of the onset of dizziness, nausea, or hypotension. In 26 other subjects the drug was stopped after one fourth to four fifths of the calculated dose because a maximum response had been attained. In most of the 40 patients the symptoms were promptly relieved by elevation of the feet, administration of oxygen, and cessation of administration of azapetine. In 5 patients a small amount of phenylephrine (Neosynephrine) was also given by slow intravenous infusion. This treatment promptly corrected any residual hypotension and abolished the symptoms. More recently we have given 50 mg. of Dramamine prior to the study, with considerable reduction in the incidence of nausea. As in the case of the medical students, very few of the ambulatory patients experienced any difficulty in standing after the customary period of half an hour after completion of the drug infusion during which they were left in the prone position.

If these precautions are followed, such temperature studies offer an excellent means of predicting the degree of vasospasm and the probable clinical effectiveness of these drugs in patients.[10] If body warming is used in addition to the blocking drug, the technic is of considerable value in predicting the probable effect of sympathectomy in patients with peripheral vascular disease.[11]

Summary

In order to evaluate the possible effectiveness of a group of adrenergic blocking drugs used in treating peripheral vascular disease, the drugs were administered to a group of 10 normal subjects in whom vasospasm had been induced and the relative degree of relaxation of the vasospasm produced by each of the drugs was compared. Blood flow and the degree of vasoconstriction and vasodilatation were estimated from temperatures recorded from the skin of the tips of the digits. The vasospasm (reflex cutaneous vasoconstriction) was induced by exposure of lightly clad subjects to a room temperature of 20 C. for an initial period of 45 to 90 min. The 4 drugs used were tolazoline (Priscoline), azapetine (Ilidar), tolazoline-phentolamine (Priscoline-Regitine) combination, and phenoxybenzamine (Dibenzyline). Ten subjects were used, each subject receiving in turn each of the 4 drugs to make a total of 40 studies.

After maximum vasospasm was induced, the drugs were administered intravenously over a period of 30 to 45 min. in the doses: tolazoline, 2 mg./Kg.; azapetine, 1 mg./Kg.; tolazoline-phentolamine, 0.75 mg. of each/Kg.; and phenoxybenzamine, 0.2 mg./Kg.; each drug was diluted in 200 ml. of 0.9 per cent saline solution. Tolazoline and azapetine were found to be fairly good vasodilators in both the upper and lower extremities with the tolazoline-phentolamine combination producing somewhat less vasodilatation and phenoxybenzamine the poorest response. There were no dangerous or painful side effects to any of these drugs, but the phenoxybenzamine was followed, some time after the drug was administered, by symptoms that suggested postural hypotension.

Acknowledgment

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The azapetine PO_4, Ilidar PO_4, (RO 2-3248) was supplied by Hoffmann-LaRoche, Inc., Nutley, New Jersey. The phenoxybenzamine, Dibenzyline, was

supplied by Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania. The tolazoline hydrochloride, Priscoline hydrochloride, and the tolazoline-phentolamine combination were supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Summario in Interlingua

Pro evalutar le efficacia possible de un gruppo de agentes de blocage adrenergic usate in le tractamento de morbo periphero-vascular, illos esseva administrate a un gruppo de 10 subjectos normal in qui vasospasmo habeva essite inducite, e le relative grado de relaxation del vasospasmo effectuate per cata un del agentes esseva comparate. Le fluxo sanguinee e le grado de vasoconstriction e vasodilatation esseva estimate super le base del temperaturas registrate al pelle del punctas digital. Le vasospasmo (reflexe vasoconstriction cutanee) esseva inducite per exponer le subjectos in leve vestimentos a un temperatura de interio de 20 C durante un periodo initial de inter 45 e 90 minutas. Le quatro agentes usate esseva tolazolina (Priscolina), azapetina (Ilidar), tolazolina e phentolamina (Regitina) in combination, e phenoxybenzamina (Dibenzylina). Cata un del 10 subjectos recipeva cata un del 4 agentes, resultante in un total de 40 studios.

Post induction del vasospasmo maximal, le drogas esseva administrate intravenosemente in le curso de periodos de inter 30 e 45 minutas. Le doses usate esseva: tolazolina, 2 mg per kg de peso corporee; azapetina, 1 mg per kg; tolazolina-phentolamina, 0,75 mg per kg de cata un; e phenoxybenzamina, 0,2 mg per kg. Cata dose esseva diluite in 200 ml de solution salin de 0,9 pro cento.

Esseva constatate que tolazolina e azapetina es satis bon vasodilatatores in le extremitates tanto superior como etiam inferior. Un vasodilatation alique inferior esseva producite per le combination de tolazolina e phentolamina. Le pejor responsa esseva obtenite per phenoxybenzamina. Nulle periculose o dolorose effectos lateral esseva notate pro ulle del drogas, sed le administration de phenoxybenzamina esseva sequite post un certe intervallo per symptomas que suggereva hypotension postural.

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A Heart Function Test with Continuous Registration of Oxygen Consumption and Carbon Dioxide Production

By J. Jongbloed, M.D., C. L. C. Van Nieuwenhuizen, M.D., and H. Van Goor, M.D.

The authors present a test of myocardial function based on the continuous registration of pulmonary exchange of oxygen and carbon dioxide during rest and a standard amount of work. The authors believe that the test is simple enough for wide clinical application. The "functiocardiogram" is of considerable physiologic and clinical interest. The normal values of the test are defined and a few examples of abnormal tests are discussed.

EVERY cardiologist would like at times to have a reliable test of heart function at his disposal. There appear to be 3 reasons why a test of heart function is so infrequently used as a routine method. First, really reliable tests of heart function are too complicated for everyday practice, with the exception perhaps of Nylin's test.[1] Second, many cardiologists believe that x-rays and electrocardiograms give sufficient information about the cardiac function, but this attitude is surely disputable. Third, cardiologists often think that the history of the disease provides sufficient information about the functional state of the heart and circulation, so that special tests of function are of little if any use. This view is only partly true. By the time breathlessness on effort or venous congestion point to impaired cardiac function, circulatory failure is already on its way; so it still seems important to search for a method that, by imposing a certain strain on the circulation, can disclose impending circulatory failure.

In 1949 a test of cardiac function was described[2] that is based on the continuous registration of pulmonary exchange of gas during rest and work. Since that time the apparatus has been developed further without change in principle. In normal healthy subjects of varying age and sex the normal values of the test were established and the test was applied in about 1,000 subjects. In this paper some tests in patients are discussed as examples; the application of the test in clinical cases is reported separately.

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It was our aim to keep the test itself, the calculations, and its evaluation as simple as possible, so that the busy clinician without a special laboratory or specially skilled workers can apply it easily. The test is performed by the patient in about 24 min., and the necessary calculations take even less time. The conduct of the experiment and the evaluation of the graph can easily be done by a skilled technician.

In a simple way and in a short time, with only 1 apparatus our test gives insight into the adaptation of the circulatory system to a given amount of work, and therewith into the functional state of the heart in a given case. The cardiac function is recorded directly on a graph. Just as the cardiologist can get an impression of cardiac disease by a single glance at an electrocardiogram, so can he get an idea of the general function of the heart with 1 gaze at our "functiocardiogram." As with the electrocardiogram, more exact information can be obtained by analysis of the graph.

Method and Apparatus

By means of a diaferometer[3] specially constructed for this purpose the oxygen consumption (and usually also the carbon dioxide production) was measured and recorded continuously during rest, during work, and again during the following rest.

To make the "functiocardiograms" easily comparable we usually followed a standard procedure. The work was performed on a bicycle ergometer or by climbing up and down a step at a fixed tempo.[4] In the first case, the work amounted to 60 watts and in the latter instance to about 50 watts, depending on the weight of the subject. This amount of work was established, in a series of experiments with normal subjects, as easily performed during 8 min. without any sign of fatigue.

First the subject sat at rest for about 8 min., then he worked for exactly 8 min., and finally rested

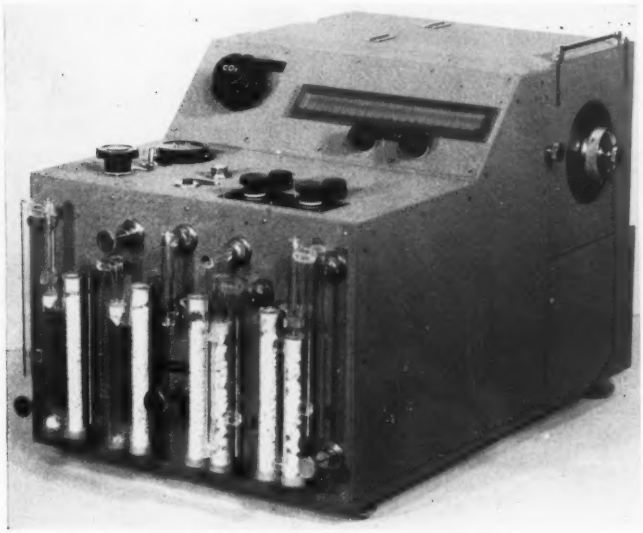

FIG. 1. Photograph of the recording apparatus

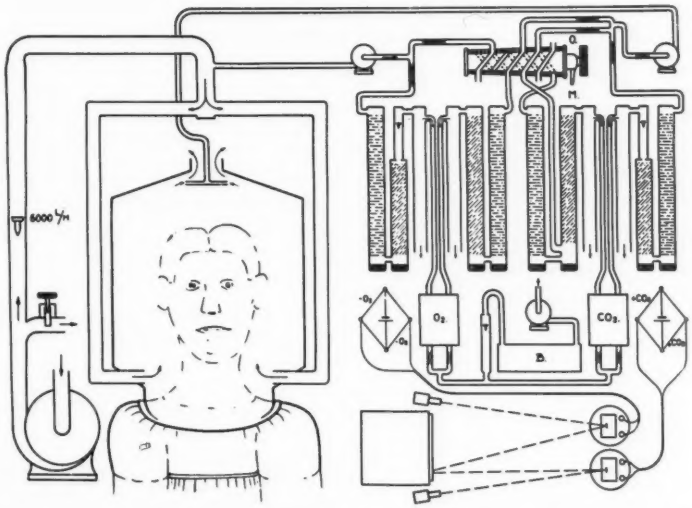

FIG. 2. Diagram of the equipment. On the left is the fan blowing outdoor air through the helmet. This air escapes freely at the top of the helmet; a small sample is continuously removed by the small pump at the top right and sent through the diaferometer. A second small pump (top, middle) delivers outdoor air for the diaferometer. The stopcock (top, right) is in the measuring position (*M*); the position *O* shown with dotted lines is for the registration of the 0 lines. The air sample passes eventually through a tube of soda-lime (horizontal shading), and through a drying tube (oblique shading). Part of the sample is sucked by the third small pump through the measuring block of the diaferometers (CO_2 and O_2) and the rest of the sample escapes freely. The blocks contain the Wheatstone bridges. In the CO_2 apparatus 2 wires receive gas with CO_2 (marked $+CO_2$), the other 2, gas deprived of CO_2. In the O_2-apparatus 2 wires marked $-O_2$ receive patient air without CO_2 (and deprived of part of the O_2), the others outdoor air without CO_2. At the bottom to the right are the galvanometers and the photographic kymograph.

again in a sitting position for 8 min. During the whole time the gas exchange was recorded continuously.

The recording apparatus is shown in figure 1, and a diagram of the whole equipment in figure 2. We used 2 types of recording apparatus, 1 recorded only oxygen consumption and the other also recorded carbon dioxide production, whereby the respiratory quotient (*R.Q.*) could also be determined. In most cases the record of oxygen consumption alone was sufficient.

In principle, the oxygen recorder consisted of 4 platinum wires forming a Wheatstone bridge, heated by a constant electric current. The wires were enclosed in slits cut in a brass block. Along these wires air samples passed continuously that were obtained in the following way. The head and shoulders of the subject were enclosed in a roomy helmet, through which outdoor air at a constant current of 100 L./min. was passed. This air was reduced in oxygen and enriched in carbon dioxide by the subject. A sample was sucked from the outgoing air, dried and deprived of carbon dioxide by soda-lime, and passed with constant speed along 2 of the platinum wires. Along the other 2 wires outdoor air, similarly dried and deprived of carbon dioxide, was passed at the same speed. The only difference between the 2 samples was the ratio between oxygen and nitrogen: the greater the difference in this ratio, the greater was the difference in the cooling of the heated wires by the air stream. The consequent change in temperature of the wires produced a change in electric resistance and a disequilibrium of the Wheatstone bridge, which was recorded by a galvanometer. The deflection of the galvanometer was calibrated so that it measured the reduction in oxygen content of the outdoor air by the subject.

To measure the carbon dioxide production of the subject a similar procedure was used. Here the dry air from the subject was compared with similar air deprived of carbon dioxide, the only difference between the samples being the carbon dioxide content.

In an apparatus without amplification, sensitive but very stable mirror galvanometers and photographic recording were used. The photographic recording could also be omitted, since the deflections of the galvanometer could be read on a scale every 30 sec. and a curve could be drawn through the assembled points. An ink-writing recorder was also used after amplification.

Functiocardiogram and Its Evaluation

Figure 3 shows the graph of a normal healthy man, 45 years old, with a very good performance on the bicycle ergometer (60 watts). The oxygen consumption during any period of the experiment was easily measured as the area above the 0 baseline. Each millimeter of de-

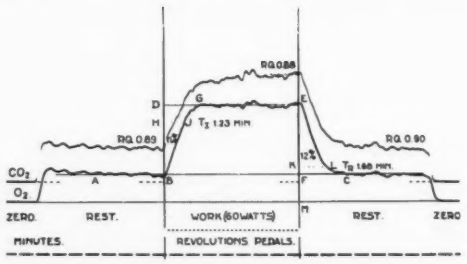

Fig. 3. The functiocardiogram of a normal subject on a bicycle ergometer at 60 watts work and airflow through the helmet of 100 L./min. The graph shows the time in minutes, the work done (each point represents 10 revolutions of the pedals), the O_2 consumption, and the CO_2 production. The 2 vertical lines mark the beginning and the end of the work.

flection of the galvanometer represented a known percentage of oxygen taken by the subject from the liters of air passing per minute through the helmet. Absolute data could then be calculated, both for oxygen consumption and carbon dioxide production. As a routine, we did not proceed in this way; for the sake of simplicity, we routinely calculated only the relative values.

The gas exchange was shown as an undulating line, rather than a steady one. Nevertheless, the average could easily be drawn (solid line *AB*) through the oxygen line of the first period of rest before the work. This line, representing the mean oxygen consumption at rest before work, was extended across the graph. At the point *C* where it intersected the oxygen line of the recovery period after the work, the oxygen consumption regained the initial resting value. At the start of the work the oxygen line went up, but it took some time for the organism to become adapted to the work. Then the oxygen line again became level: the subject was then in the "steady state" so far as the oxygen uptake was concerned. Through this more or less undulating oxygen line the average line *DE* was drawn. With a planimeter or any other suitable method the areas of the 3 figures *BDG*, *BGEF*, and *FEC* were measured. The area *BGEF* represented the extra oxygen consumption above the resting value during the *work*; we call it O_W. Area *FEC* represented the extra oxygen consumption

during the *recovery*; it is the total oxygen debt and we called it O_R. The sum of O_W and O_R constituted the total extra oxygen consumption needed for the work. Area *BDG* represented the quantity of oxygen that was lacking in the adaptation period; we called it the *initial* oxygen debt, or O_I.

Of special interest were the initial debt (O_I) as a measure of the adaptation to the work and the total debt (O_R) as an indication of how well the oxygen uptake per minute in the steady state covered the oxygen requirement. To obtain relative values the initial debt (O_I) and the total debt (O_R) were expressed as percentages of the total extra oxygen consumption ($O_W + O_R$). The quotient $\frac{O_I \times 100}{O_W + O_R}$ was called Q_I (per cent) and the quotient $\frac{O_R \times 100}{O_W + O_R}$ was called Q_R (per cent). The same procedure was, in principle, followed by Kaplan and Kaplan.[5]

From figure 3 in this way we found the Q_I to be 11 per cent and Q_R to be 12 per cent. Thus the initial debt during the adaptation period amounted to 11 per cent of the total extra oxygen consumption, and the total debt to 12 per cent. The values were rounded off to whole figures, since errors in measuring the areas made the decimal places invalid. Therefore, we may say that in figure 3 Q_I and Q_R were essentially alike; this means that this subject did not develop any extra oxygen debt during the steady state, in other words he covered his oxygen requirement per minute.

If the subject had clinically normal lungs, we may say that the oxygen uptake was a function of the amount of blood passing through the lungs, that is, of the cardiac output. Under such circumstances the graph, which we called the "functiocardiogram," reflected the work done by the heart.

If the function of the heart was normal, its work was soon adapted to the standard amount of work imposed upon it, so that the initial debt (O_I) was small in relation to the extra oxygen consumption; furthermore, since this work was very moderate, the oxygen consumption in the steady state covered the oxygen requirement, so that the total debt (O_R) was almost equal to the initial debt.

On the other hand, if the function of the heart was subnormal for any reason, adaptation to work was slower, so that the initial debt (O_I) was abnormally large. Furthermore, a truly steady state may not be reached. Instead, the oxygen uptake might stop at a level that was too low to cover the oxygen requirement; as a result the total debt (O_R) might be higher than the initial debt (O_I).

In summary, it is possible to conclude from the general appearance of the oxygen consumption curve whether or not the cardiac function was normal, and to gain more exact information by expressing O_I and O_R in percentage of the total extra oxygen consumption during work.

The curve of carbon dioxide production may be treated in the same way as the oxygen line. Although it may give valuable information in some cases, we did not as a rule use it, but usually simply determined the respiratory quotient at the end of the working period in the following way. The elevations above their 0 lines of the oxygen and carbon dioxide lines at the end of the work were measured. In the original graph of figure 3 the values were 62.2 mm. for the vertical distance *ME* between the 2 solid lines for oxygen, and 69.0 mm. for the distance between the dotted 0 line at *F* and the uppermost dotted line for carbon dioxide. On this graph 1 mm. represented 0.0176 per cent for oxygen and 0.0144 per cent for carbon dioxide. Since the external air flowing through the helmet contained 0.03 per cent carbon dioxide, 2 mm. $\left(\frac{0.03}{0.0144}\right)$ was subtracted from the measured carbon dioxide. Thus the work *R.Q.* was

$$\frac{(69.0 - 2.0) \times 0.0144}{62.2 \times 0.0176} \text{ or } \frac{69.0 - 2.0}{62.2} \times 0.818 = 0.88.$$

The factor 0.818, once determined, was fixed for the apparatus. This *R.Q.* during work supported the conclusions drawn from the values of Q_I and Q_R. In normal subjects, who performed this moderate work easily, the *R.Q.* of the steady state was almost similar to the resting *R.Q.*,

with a possible slight rise above the resting value. But in subjects with heart failure, who may develop a relative lack of oxygen during work, lactic acid may accumulate in the blood and liberate carbon dioxide from bicarbonate. In such cases the expired carbon dioxide was derived not only from combustion, but also from bicarbonate; therefore the *R.Q.* may rise above 1.00.

In the case of the normal subject of figure 3 the *R.Q.* of work or steady state amounted to 0.88, a normal value. This steady state *R.Q.* could be compared with the *R.Q.* in the resting period before work and at the end of the recovery period. In figure 3 the 3 *R.Q.*'s were about the same: 0.89, 0.88, and 0.90. Since the excursion of the galvanometers in both the resting periods was small (in most cases less than 20 mm.), a slight inaccuracy in measuring the elevations might result in large errors of the *R.Q.* Therefore we usually restricted ourselves to the *R.Q.* at the end of the work, which is surely the most interesting of the 3.

There are 2 more values we liked to determine in the functiocardiogram: The time between the beginning of the work and reaching the steady state of oxygen uptake (adaptation time), and the time between the end of the work and the return of the oxygen consumption to the original resting value (recovery time). These were the distances *DG* and *FC* in figure 3. In most cases, however, these values could not be obtained exactly, since the points of interception *G* and *C* were too dependent on local undulations of the oxygen line. These variations made very little difference in the areas *FCE* and *DGE*, but made large differences in the adaptation and recovery times. Therefore we did not determine these times by measuring *DG* and *FC*, but we arbitrarily chose other less variable distances. For the adaptation time we measured the time from the start of work until the extra oxygen uptake reached a value 25 per cent less than in the steady state of oxygen uptake. For the recovery time we took the time elapsed after the end of the work until the oxygen consumption was 25 per cent above the average resting value before work. Thus in figure 3 $DH = \frac{1}{4} BD$, and $FK = \frac{1}{4} FM$, and the dotted lines *HJ* and *KL* gave the initial time (T_I) and the recovery time (T_R) in minutes. These times were not really the initial and the recovery times, but only arbitrary intervals, which, however, could be measured exactly and could be compared in normal and abnormal subjects. In figure 3 $T_I = 1.23$ min. and $T_R = 1.68$ min.

Functiocardiogram in Normal Subjects

The normal values of the different characteristics of the functiocardiogram were determined in standard tests (60 watts for 8 min.) on 30 normal men and 15 normal women between 18 and 50 years of age. The results are shown in table 1.

In table 1 the average value of Q_R is about 1 per cent higher than Q_I, but the difference is not significant, that is, in these normal subjects $Q_I = Q_R$, as indeed it should be. Only 1 man and 3 women had a Q_R above 17 per cent.

In women Q_R (total oxygen debt) was about 1 per cent higher than in men, but for the sake of simplicity the same standard may be used for both sexes and for ages between 18 and 50 years. It appears that a Q_R of 15 per cent was about the average normal value; values below 15 per cent were very good and the upper limit of normal was 17 per cent. The same values apply to Q_I (initial debt). In individual normal cases the same figure was not always found for Q_I and Q_R; small differences may easily occur in the living subject. Since the difference between Q_I and Q_R was seldom more than 2 per cent in our 45 normal subjects, a difference of 2 per cent or less was considered normal and a difference of 3 per cent was borderline.

The "initial time" (T_I) and the "recovery time" (T_R) determined arbitrarily as described were also higher in women than in men (table

Table 1.—*Average Values in Normal Subjects between Eighteen and Fifty Years*

Number of subjects	Q_I (%)	Q_R (%)	T_I (min.)	T_R (min.)	Respiratory quotient at end of work
30 men	14.0	15.0	1.50	2.09	0.89
15 women	15.6	16.3	1.66	2.32	0.93
45 total	14.5	15.4	1.55	2.17	0.90

1). For practical reasons this difference was also ignored. Since only 1 normal man and 3 women had a T_I slightly above 1.80 min., we took 1.80 min. as the normal limit for T_I. The normal limit for T_R was fixed at 2.50 min., there being only 2 men and 3 women of our normal subjects who exceeded this value slightly.

As might be expected, the average *R.Q.* at the end of the work (table 1) was well above the average *R.Q.* in men under basal conditions. In all normal subjects it was below 1.00, however, with a mean of 0.90.

To test the reproducibility of our standard heart function test (60 watts, 8 min.) we performed 16 experiments each with 2 subjects on successive or alternate days over a month's time. As might be expected, table 2 shows that the values varied from day to day. These differences seem reasonable for tests that were expressly not done under basal conditions, since it was desired to use the test in everyday practice. All results of both subjects were normal except 1 borderline value (Q_R = 16.7 per cent).

Amount of Work

A standard work load of 60 watts for 8 min. was used in all the tests in establishing normal standards and in evaluating cardiac patients. The amount of work chosen was very moderate, it required about 1 L. extra of oxygen per minute. Normal subjects could very easily get this quantity, but cardiac patients had more difficulty with it.

If the amount of work were too small, there would be little difference between the curves of normal and cardiac patients. If, on the other hand, the work were heavy, most patients would not be able to do it. Most of the cardiac patients could perform this standard work with more or less difficulty. Some patients could not keep up the work for 8 min. and stopped early. All patients were told to stop if they felt tired. This fact alone proved that their cardiac function was below normal.

Instead of imposing a standard work load, one could determine the maximum work capacity of a patient and compare it with normal standards. We did not choose this as a routine method, because we did not like to subject all our cardiac patients to exhausting work, and because in such cases the psychic behavior, the will to proceed, would greatly influence the performance.

The bicycle ergometer is not entirely necessary; the test was not altered materially by the subject climbing up and down a step at a fixed tempo. With the ergometer the amount of work was the same for all subjects, whereas in stair climbing the amount of work depended on the body weight.

In figure 4 is a graph obtained from a normal subject while going up and down a step of 20 cm. every 4 sec. for 8 min. With a body weight of g Kg., the work with every step up was 0.2 g Kg.M. If the work for the step down is taken as one third of the step up, the total work in every cycle of 4 sec. is $\frac{4}{3} \times \frac{1}{5}g$Kg.M. Per second the work is $\frac{1}{4} \times \frac{4}{3} \times \frac{1}{5}g$Kg.M. or $\frac{1}{15} \times g \times 10$ watts $= \frac{2}{3}g$ watts. The work in watts thus equals two thirds of the body weight in Kg.

The body weight of the subject of figure 4 was 84 Kg.; thus the work performed was $\frac{2}{3} \times 84 = 56$ watts. Similarly, in most subjects, the work of the step test was less than the 60 watts of the bicycle test. We did not use a higher step or a faster cycle because the total extra oxygen consumption was higher in the step test than in the bicycle test due to its lower mechanical efficiency.

Table 2.—*Minimum, Maximum, and Average Values of Sixteen Experiments in Each of Two Normal Subjects*

Subject	Q_I %	Q_R %	T_I min.	T_R min.	Respiratory Quotient
A	9.0 – 14.2	11.7 – 14.1	0.97 – 1.57	1.59 – 2.10	0.82 – 0.94
	11.4 ± 1.5	12.7 ± 0.7	1.25 ± 0.16	1.80 ± 0.16	0.88 ± 0.03
B	12.9 – 15.7	13.2 – 16.7	1.31 – 1.59	2.01 – 2.68	0.86 – 0.98
	14.1 ± 0.9	15.3 ± 1.1	1.46 ± 0.08	2.34 ± 0.18	0.91 ± 0.04

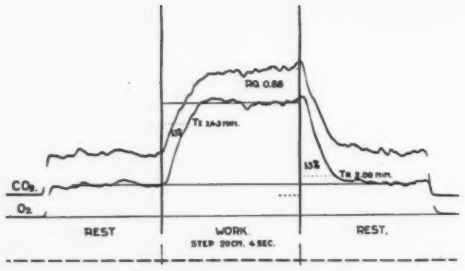

FIG. 4. Functiocardiogram of a normal subject stepping on and off a step of 20 cm. every 4 sec. Body weight 84 Kg., work 56 watts during 8 min., airflow through helmet 100 L./min.

DETERMINATION OF ABSOLUTE OXYGEN VALUES

The routine use of the *relative* values (Q_I and Q_R) together with the times, T_I and T_R and the work *R.Q.* gave sufficient information for evaluating the results, and their determination required only little calculation and little time. The areas of the 3 parts of the graph had to be measured. This was easily done with a planimeter, but for most purposes a special instrument was not needed. With an ink-writing apparatus the curve could be drawn directly on graph paper divided in 1 cm.² squares; with photographic apparatus the curve could be redrawn on graph paper by transillumination (fig. 5). Where the curve crossed a square the fraction belonging to each area could be estimated with sufficient accuracy.

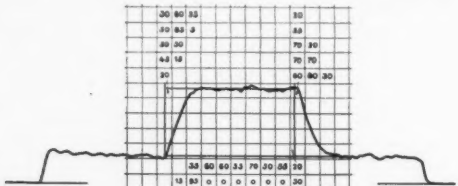

FIG. 5. The oxygen curve of figure 3 redrawn on a paper with squares of 1 cm.² The estimated areas (in mm.²) of the parts of the squares belonging to O_I and O_R are noted on top, those belonging to O_W on the bottom. The plain squares (100 mm.²) are marked with *O*. The estimated total area of O_I is 435 mm.², of O_R 475 mm.², and of O_W 3,470 mm.² Calculations of these figures shows Q_I to be $\frac{435}{3{,}470 + 475} \times 100$ per cent = 11 per cent and $Q_R \frac{475}{3{,}470 + 475} = 12$ per cent, that is, the same values as found by planimetry.

Various *absolute* values could also be obtained from the graph, such as the oxygen debt and the oxygen uptake per minute during the work and the maximum oxygen uptake per minute if the subject worked to exhaustion. To evaluate absolute values the procedure was as follows. For the apparatus used in figure 3 the oxygen factor was 0.0176, that is, a vertical deflection of 1 mm. on the original graph corresponded to 0.0176 per cent of oxygen. The speed of the paper was 11 mm./min. Since 100 L. of air passed through the helmet per minute, a galvanometer deflection of 1 mm. during 1 minute, i.e., an area of 11 mm.², represented an oxygen consumption of 0.0176 per cent of 100 L. or 17.6 ml. In this case each mm.² of area stood for $\frac{17.6}{11}$, or 1.6 ml. oxygen, and any area in mm.² multiplied by 1.6 gave the oxygen consumption in the period concerned directly. The height of the oxygen line in mm. above the 0 line multiplied by 17.6 gave the total oxygen consumption per minute at that moment. These values of course required correction for pressure, temperature, and humidity.

In our normal subjects the average surface of $O_W + O_R$ (i.e., the total extra oxygen consumption needed for the work of 60 watts during 8 min. on the bicycle ergometer) was about 4,000 mm.². This corresponded to 4,000 × 1.6 = 6,400 ml. oxygen. Since 60 watts equal about 6 Kg.M./sec., the total amount of work is 8 × 60 × 6 Kg.M. = 2,880 Kg.M. The caloric value of 1 ml. oxygen being about 5 calories or 5 × 0.426 Kg.M. = 2.13 Kg.M., the mechanical efficiency was $\frac{2880}{6{,}400 \times 2.13} \times 100$ per cent = 21 per cent.

RESPIRATORY QUOTIENT

In many cardiac patients the *R.Q.* was above 1.00 at the end of the 8 min. of work. This means that the oxygen uptake during the work did not cover the oxygen requirement. For those patients the standard work represented severe work. It is clear that the same high *R.Q.*

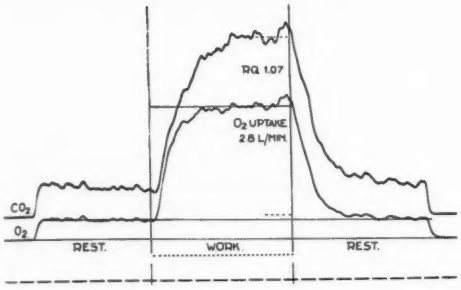

FIG. 6. Functiocardiogram of a normal subject on the bicycle-ergometer. Work 180 watts during 8 min. R.Q. at the end of the work 1.07; oxygen-uptake in the "steady state" 2.8 L./min. Airflow through the helmet 200 L./min.

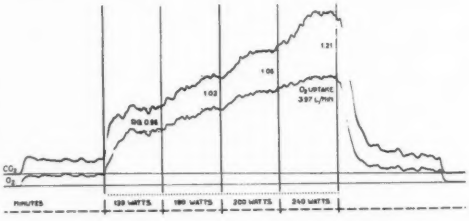

FIG. 7. Functiocardiogram of a normal subject on the bicycle ergometer with increasing load. Airflow through helmet 233 L./min. The work *R.Q.* increased to 1.21; oxygen uptake at the highest load 3.97 L./min.

may appear in normal subjects if they perform severe work. Figure 6 gives an example of an experiment in a normal subject on the bicycle ergometer in which the work performed for 8 min. was 180 watts. The work *R.Q.* amounted to 1.07. Since the airflow through the helmet in this case was 200 L./min. and the oxygen deflection after the adaptation to the work was 80 mm., the oxygen uptake in this period amounted to $80 \times 0.0176 \times \frac{200}{100} = 2.8$ L./min.

Figure 7 represents the result of an experiment on the bicycle ergometer in a normal subject in which the work was increased step by step, until the subject was near exhaustion. In the first period the work was 120 watts and the work *R.Q.* was 0.96; in the second period the work was 160 watts and the *R.Q.* 1.02; in the third the figures were 200 watts with *R.Q.* of 1.06; and in the last, 240 watts with *R.Q.* of 1.21. At the end of the last period the subject thought that he was at his maximum load and we concluded that his oxygen uptake was maximal. Since the flow of air through the helmet was 233 L./min. in this case and the deflection of the galvanometer on the original graph at the end of the last period was 97 mm., the maximal oxygen uptake of the subject was $97 \times 0.0176 \times 2.33$ L. = 3.97 L./min. The total oxygen debt as estimated from the surface O_R was about 5 L., which proved indeed that the subject was not quite exhausted but near to it; he said he might have gone for some minutes more. By continuing the work his debt shortly would have grown to its maximum.

SOME FUNCTIOCARDIOGRAMS OF PATIENTS

The functiocardiogram of patients with different kinds of heart diseases will be extensively described in subsequent publications. Here we wish to show some graphs differing from normal.

Figure 8 shows the graph of a female patient with mitral stenosis but with only slight complaints. She reached the steady state a bit late; Q_I = 19 per cent, Q_R = 20 per cent, both

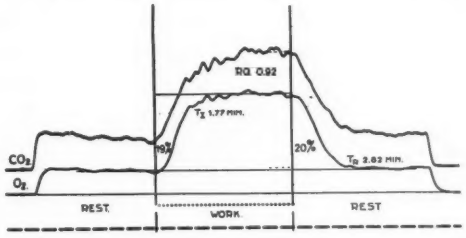

FIG. 8. Functiocardiogram of a patient with mitral stenosis and slight complaints. Bicycle-ergometer, 60 watts, airflow 100 L./min.

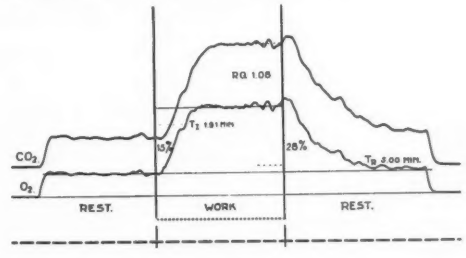

FIG. 9. Graph of a patient with mitral stenosis and moderate complaints. Bicycle-ergometer 60 watts, airflow 100 L./min.

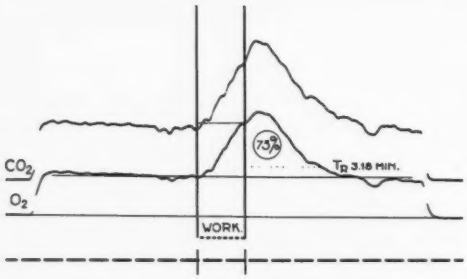

FIG. 10. Graph of a patient with mitral stenosis and very serious complaints. Bicycle-ergometer 60 watts, airflow 100 L./min. Work stopped after 2 min.

are too high. They are equal, so that the oxygen uptake per minute in the steady state covered the requirement; correspondingly, the *R.Q.* was normal at 0.92. The conclusion is that the cardiac function at this amount of work (60 watts, 8 min.) was below normal.

Figure 9 is the functiocardiogram of a patient with mitral stenosis with more complaints. He reached what seemed to be a steady state with a normal initial debt (Q_I = 15 per cent); thus the adaptation to the work seemed normal. However, since the total oxygen debt was much greater (Q_R = 28 per cent), he did not cover his requirement during the "steady state" but made an extra debt. It seems that he was at the limit of his oxygen uptake; the *R.Q.* in this period of 1.08 was in agreement. The recovery time was also too long. The cardiac function was far below normal.

Figure 10 is the graph of a female patient with mitral stenosis with very serious complaints. She could sustain the work of 60 watts for only 2 min. She did not reach a steady state, and it appears from the graph that the total oxygen debt was 75 per cent of the total extra oxygen consumption needed for the work; that is, three quarters of this small amount of work was done on credit. The "recovery time" (3.18 min.) was extremely long for the work done. This is an example of very bad cardiac function.

Figure 11 shows the graph of a woman with cardiac complaints in which the cardiologist could not find clinical cardiac disease. She stopped the work (60 watts) after 5 min. The Q_I was 20 per cent and the Q_R 24 per cent of

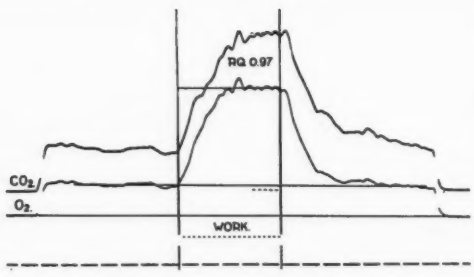

FIG. 11. Functiocardiogram of a woman with cardiac complaints without clinical evidence of heart disease. Bicycle-ergometer 60 watts, airflow 100 L./min. Work stopped after 5 min., very probably prematurely.

the total extra oxygen consumption during this 5 min. of work. Of course these percentages are not directly comparable with the usual percentages for 8 min. of work. The patient reached a steady state; if she had continued the work for 3 min. more, at the same rate, Q_I would have been about $\frac{5}{8} \times 20$ per cent = $12\frac{1}{2}$ per cent and Q_R $\frac{5}{8} \times 24$ per cent = 15

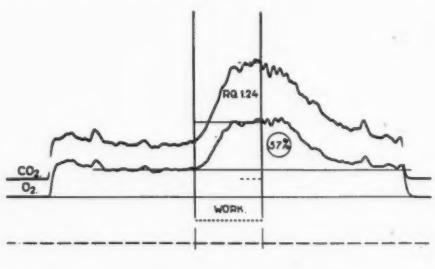

FIG. 12. Functiocardiogram of a patient with mitral stenosis before surgery. Bicycle-ergometer 60 watts, airflow 100 L./min. The work was stopped after 4 min.

FIG. 13. Same patient as in figure 12 after operation. Bicycle-ergometer 60 watts, airflow 100 L./min. The different values were still too high, but the graph indicated that the condition of the patient was much improved.

per cent. These latter values would have been within the normal range, and the difference between Q_I and Q_R would also have been normal, though borderline. From these observations we may conclude that the oxygen requirement per minute was covered by the oxygen uptake in the steady state. The *R.Q.* at the end of the steady state was 0.97, a rather high value but below 1.00; thus the *R.Q.* did not indicate failure to cover the oxygen requirement. Everything seemed to be rather normal and the functiocardiogram gave no reason why the patient stopped the work after 5 min. This was in agreement with our impression that the patient was not exhausted after 5 min. of work. The conclusion must be that she stopped the work prematurely.

Figures 12 and 13 show functiocardiograms of a patient with mitral stenosis before and after cardiac surgery. Preoperatively (fig. 12) the patient had to stop work (60 watts) after 4 min.; about 60 per cent of this small amount of work was delivered on credit and the "recovery time" was very long (5.0 min.). At the end of the work the *R.Q.* was 1.24, proving that the oxygen requirement was not met. From this graph it appears that the heart function was bad.

After the operation (fig. 13) the patient could perform the same work (60 watts) without distress for 8 min. The function of the heart was not yet normal, for Q_I of 20 per cent and Q_R of 19 per cent were both too high, but their equality meant that the oxygen requirement per minute was covered in the steady state, as was indicated by the *R.Q.* of 0.92 at the end of the work. According to this improvement in the graph the patient gained much by the surgery. This impression was in close agreement with the clinical observations of the cardiologist.

Summary

A heart function test is described that was applied in about 1,000 cases. The apparatus was based on the principle of the diaferometer and gave the results in a graph. The evaluation of the graph was kept as simple as possible, to make it apt for clinical use where there is little accommodation for extensive experimental work.

Summario in Interlingua

Es describite un test de function cardiac que esseva applicate a circa 1.000 casos. Le apparatura utilisa le principio del diaferometro e presenta su resultatos in un forma graphic. Le evalutation del graphico esseva rendite le plus simple possible pro assecurar le usabilitate del methodo pro objectivos clinic sub conditiones que non offere facilitates pro extense labores experimental.

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Let us now peruse our ancient authors, for out of the old fields must come the new corn.—Edward Coke, 1552–1634.

Alveolar Walls in Mitral Stenosis

By Robert M. O'Neal, M.D., Wilbur A. Thomas, M.D., Kyu Taik Lee, M.D., and Erwin R. Rabin, M.D.

Pathologic alterations of alveolar walls in 95 autopsied patients with mitral stenosis were not frequent. The most frequently encountered change was capillary dilatation, and in 83 per cent of the patients, even this change was slight or absent. Other alterations were focal and involved only small proportions of the area of tissue examined. A generalized increase in the thickness of basement membranes could not be demonstrated.

PATHOLOGIC changes in the pulmonary alveolar walls of patients with mitral stenosis have been described by many investigators.[1–3] Among the changes described are fibrous thickening, capillary distention, thickening of the capillary basement membranes, and cuboidalization of the alveolar lining cells. It has been pointed out that such pathologic alterations, if widespread, could produce marked physiologic disturbances.[4] However, our own observations on current autopsies of individual patients with mitral stenosis led us to suspect that advanced pathologic changes in the alveolar walls were almost always focal, rather than widespread. These observations stimulated us to review sections of the lungs from a large number of autopsied patients with mitral stenosis. The purpose of this study is to establish the extent and character of abnormalities of alveolar walls in 95 adult patients who died with mitral stenosis.

Material and Methods

Autopsy records and microsections were examined from 95 patients with mitral stenosis as a principal anatomic diagnosis. These patients represent a consecutive series of all such patients over 20 years of age, autopsied at Washington University during the period 1938 to 1954, from whom suitable material was available for study.

Patients were chosen for inclusion in the study on the basis of objective anatomic findings. The average age of the patients was 47 years. A review of the clinical and autopsy records revealed that in 90 of the 95 patients mitral stenosis was the principal abnormality present and the only apparent underlying cause of death. Congestive heart failure was extremely common among the patients, but exact figures of its incidence and duration were difficult to obtain because some of the patients entered the hospital in a terminal state, unable to give an adequate history, and often the records simply stated that the patients had been "in failure for years." At least 84 of the 95 patients had been in congestive heart failure at some time, 53 for a year or more, and 25 for 3 years or more.

The paraffin blocks of tissue from the lungs of these patients were recut and stained with aldehyde-fuchsin-van Gieson-iron hematoxylin, in order to better demonstrate fibrous and elastic tissue. Sections of lung were also stained with hematoxylin and eosin and in many instances with periodic acid-Schiff and Heidenhain's stains in order to define more clearly the various components of alveolar walls. All of these stains are as described by Lillie,[5] except for minor modifications. The microsections were examined and various features were recorded including capillary dilatation, fibrosis of the alveolar walls, thickening of capillary basement membranes, and cuboidalization of alveolar lining cells.

Comparative control material was obtained from 106 adult patients who died with a clinical diagnosis of "hypertension" and who had a principal anatomic diagnosis of arteriolar nephrosclerosis (hypertensive group) and from 50 adult patients without chronic pulmonary or cardiovascular disease (normal control group). The sections of lung stained with hematoxylin and eosin from these patients were examined and the extent and degree of capillary dilatation were recorded.

Results

Generalized fibrous thickening of pulmonary alveolar walls was not seen in any patient in this series. Focal areas of lung in which the alveolar walls contained increased amounts of fibrous tissue were present in 9 per cent of pa-

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Dr. Lee is a Life Insurance Medical Research Fund Fellow.

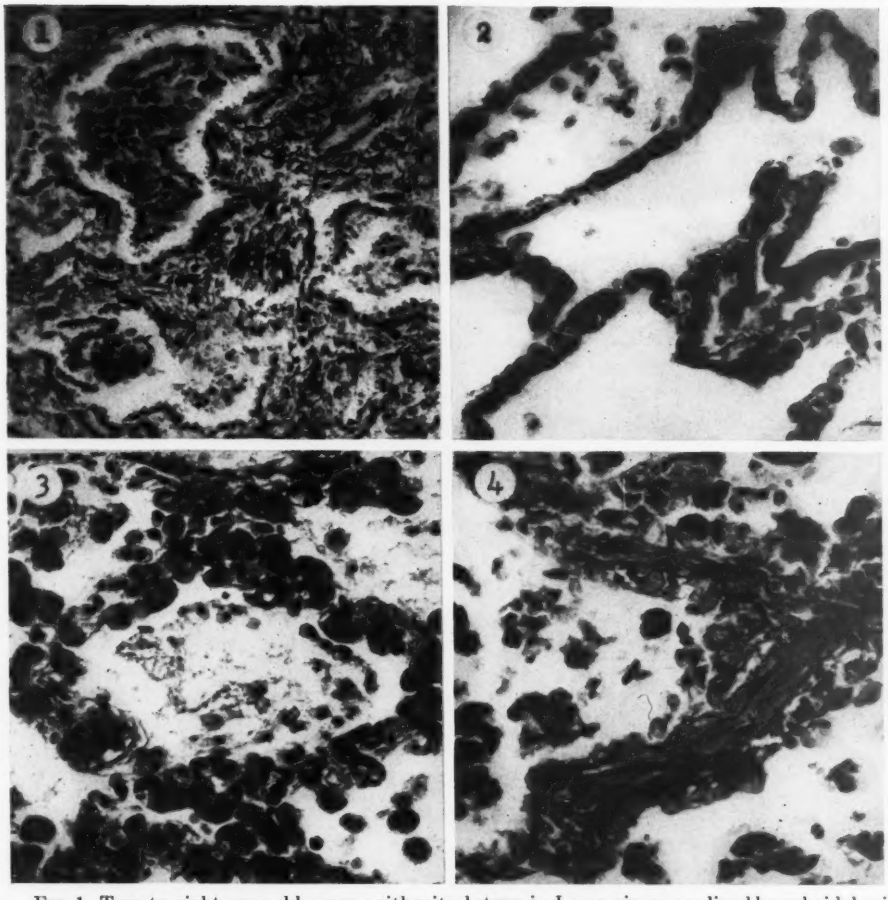

FIG. 1. Twenty-eight-year-old woman with mitral stenosis. Large air spaces lined by cuboidal epithelium and separated by thick walls of connective tissue. The air spaces contain numerous macrophages, filled with hemosiderin. The thick walls are composed of relatively avascular fibrous tissue. Relatively normal pulmonary parenchyma was seen nearby. Aldehyde fuchsin-van Gieson-iron hematoxylin stain, × 130.

FIG. 2. Thirty-seven-year-old man with mitral stenosis. Normal, slightly collapsed, pulmonary air spaces and alveolar walls. Most of the alveolar walls of the patients with mitral stenosis were not altered. Heidenhain stain, × 270.

FIG. 3. Twenty-eight-year-old woman with mitral stenosis. Advanced capillary distention in alveolar walls. Hematoxylin and eosin stain, × 300.

FIG. 4. Same patient as figure 2. An atrial sphincter muscle cut longitudinally. This can be mistaken on hematoxylin and eosin stained sections for fibrosis of alveolar walls if the anatomic relationships of peripheral air spaces are not considered. Aldehyde fuchsin-van Gieson-iron hematoxylin stain, × 360.

tients with mitral stenosis, but in extent never exceeded 10 per cent of the area of tissue examined. These focal areas were often associated with intra-alveolar accumulations of hemosiderin-filled macrophages, and were demonstrated most clearly with the Heidenhain and van Gieson stains (figs. 1, 4). Occasionally organized thrombi were seen in small pulmonary arteries adjacent to areas of fibrosis.

Cuboidal epithelium frequently lined the alveoli in the focal areas of fibrous thickening, but this change was never isolated and never

involved more than 10 per cent of the pulmonary parenchyma examined.

Thickening of the "alveolar" and capillary basement membranes was also confined to the areas of focal fibrosis of alveolar walls. Periodic acid-Schiff stains failed to reveal a generalized change in the thickness or character of these basement membranes (fig. 2).

Capillary dilatation was the most common change noted in the alveolar walls (fig. 3), but it was slight in most patients. Moderate or advanced capillary dilatation was observed in 17 per cent of the patients with mitral stenosis, in 15 per cent of the patients in the hypertensive group, and in 4 per cent of the patients in the normal control group. In none of the patients of any group did the dilated capillaries appear to encroach appreciably on the alveolar air spaces.

Discussion

Morphologic alterations (other than capillary congestion) in the alveolar walls of 95 patients with mitral stenosis were found to involve only small portions of the pulmonary parenchyma. Fibrous thickening of alveolar walls, thickening of capillary basement membranes, and cuboidal cells lining the alveoli have been described by many observers in the lungs of patients with mitral stenosis.[1, 3, 4] We were able to demonstrate these features in some of our patients. However, most of our patients did not show such changes and in the few that were affected these features were focal. It seems unlikely that alterations of the alveolar walls involved enough of the lungs to be of physiologic significance.

Pulmonary capillary distention was prominent in some of our patients, but the lack of constancy of this capillary distention in association with mitral stenosis, as well as its occurrence in other diseases, indicates that it is not a special feature of mitral stenosis. Pulmonary capillary distention could be related to increased pulmonary venous pressure from any cause, and perhaps to other physiologic disturbances occurring in the agonal state.

Goodale and his associates recently studied biopsies of lung from patients with mitral stenosis, taken at the time of mitral valvulotomy, and found that the increased resistance to pulmonary blood flow in patients with mitral stenosis did not correlate significantly with alterations in the structure of alveolar walls.[2] This observation is consistent with our conclusion that changes in alveolar walls are in general not sufficiently widespread and severe to be of physiologic importance.

The results of our study indicate that the advanced pulmonary parenchymal changes illustrated herein and described by others[1-3] are generally focal and not truly representative of the entire lungs of patients with mitral stenosis.

Pathogenesis of the Focal Fibrosis of Alveolar Walls. Even if the physiologic importance of the focal fibrous thickening and cuboidal epithelization of alveolar walls in patients with mitral stenosis is denied, their pathogenesis remains of great interest and warrants discussion, and the presentation of additional, related observations.

Occasionally, an organized, recanalized thrombus is seen in a small pulmonary artery adjacent to a focal area with thickened, fibrous, alveolar walls, suggesting that this thickening may be the result of incomplete infarction of the lung with organization of exudate adherent to the alveolar wall. Intra-alveolar fibrous bodies representing organized exudate are sometimes present and offer some support to this hypothesis. Other support is offered by the similarity of these focal areas of fibrosis in alveolar walls to the pathologic changes in the pulmonary parenchyma surrounding a healed or healing infarct.

Focal accumulations of hemosiderin-filled macrophages are often present in the alveoli that have thickened, fibrous walls, and this fibrosis may be a reaction to the iron pigment.

Another possible explanation for the formation of these focal lesions of alveolar walls is the organization of material that exuded from the capillaries into the interstitial space of the alveolar walls. This interstitial space, easily demonstrable by electron microscopy,[6] is so narrow that it cannot be seen in normal lungs with light microscopy but, with the exudation of edema fluid and fibrin, it could be expanded and organization of this exudate could occur. Parker and Weiss[1] described "pericapillary edema" of the alveolar walls in patients with

mitral stenosis, which presumably represents an expansion of the narrow interstitial space of alveolar walls by the exudation of fluid constituents of the blood. We have noted this "pericapillary edema" only rarely and even in these instances, only in occasional, short segments of alveolar walls. However, the possible frequent occurrence of lesser degrees of chronic interstitial edema, not readily demonstrable by light microscopy, cannot be excluded.

Finally, there is the possibility that the focal fibrosis of alveolar walls represents healed "rheumatic pneumonitis." Extravasation of fibrin into alveoli, frequently with the formation of "hyaline membranes" lining air spaces, is common in fatal cases of acute rheumatic fever,[7] and probably is present to some extent in many nonfatal cases. The organization of this exudate, especially that applied to the walls of air spaces in the form of a hyaline membrane, could explain the focal increase in fibrous tissue in alveolar walls that sometimes accompanies mitral stenosis.

Summary

Pathologic changes in alveolar walls have been described in the lungs of patients with mitral stenosis by many investigators. The purpose of this study is to establish the extent and character of such abnormalities of alveolar walls in 95 autopsied patients who died with mitral stenosis.

A study of microsections of the lungs of these patients reveals that pathologic alterations of alveolar walls are not frequent. Except for capillary dilatation, the changes are focal and affect only a small proportion of the area of lung examined. In 83 per cent of 95 patients even capillary dilatation was slight or absent.

These results suggest that advanced pathologic alterations of alveolar walls associated with mitral stenosis are in general only focal and are not extensive enough to be of physiologic significance.

Summario in Interlingua

Alterationes pathologic del parietes alveolar in le pulmones de patientes con stenosis mitral ha essite describite per multe investigatores. Le objectivo del presente studio es establir le grado e le character de tal anormalitates del parietes alveolar in 95 necropsiate patientes, morte con stenosis mitral.

Le studio de microsectiones del pulmones de iste patientes revela que alterationes pathologic del parietes alveolar non es frequente. A parte le dilatation capillari, le alterationes es focal e affice solmente un parve portion del area pulmonar examinate. In 83 pro cento del 95 patientes, mesmo le dilatation capillari esseva leve o completemente absente.

Iste resultatos suggere que avantiate alterationes pathologic del parietes alveolar in association con stenosis mitral es generalmente solmente focal e non satis extense pro assumer signification physiologic.

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SYMPOSIUM

THE U WAVE OF THE ELECTROCARDIOGRAM

INTRODUCTION

By EUGENE LEPESCHKIN, M.D.

THE U wave of the electrocardiogram has received but little attention in clinical electrocardiography because its significance was not clear. However, during the last 15 years an increasing number of reports has appeared in which changes of the U wave were found to be the chief clue leading to the correct clinical diagnosis. The development of intracellular electrography during the last few years has also made it possible to obtain considerable information concerning the significance and electrophysiologic basis of the U wave.

In order to summarize our knowledge concerning the U wave and to further this knowledge through informal discussion among the investigators who have studied it, a symposium on the U wave was held on September 11, 1954, in Burlington, Vermont. It was sponsored by the Vermont Heart Association and the University of Vermont College of Medicine, and featured outstanding European as well as American speakers.

It was originally planned to publish the entire proceedings of the Symposium in this Journal. However, the great length of the manuscripts made it necessary to select for publication only those presentations that contain observations not previously reported elsewhere, to abbreviate some of the papers, and also to exclude the discussion that took place at the end of each paper. It is planned to publish the full proceedings of the Symposium in monograph form.

PAPERS PRESENTED AT THE SYMPOSIUM

Papers marked by an asterisk (*) appear in this issue, partly in abbreviated form.

I. Definition and Measurement of the U Wave, *E. Lepeschkin, M.D.*, (With comments by E. Bozler, M.D., D. Littman, M.D., J. H. Palmer, M.D., C. Papp, M.D., T. Sjostrand, M.D., and B. Surawicz, M.D.)

*II. Various Types of Fusion between the T and U Waves, *Max Holzmann, M.D.*

III. The Afterpotentials of the Frog's Heart, *Marcel Segers, M.D.* (With comments by S. Bellet, M.D., E. Bozler, M.D., E. Lepeschkin, M.D., and L. Nahum, M.D.)

IV. Nonpropagated Action Potentials of Cardiac Muscle, *Emil Bozler. M.D.* (With comments by E. Lepeschkin, M.D., L. Nahum, M.D., F. Sichel, Ph.D., and B. Surawicz, M.D.)

V. The Intracellular Afterpotentials of the Heart and Their Interpretation, *E. Lepeschkin, M.D.* (With comments by H. H. Hecht, M.D., M. Kleinfeld, M.D., W. Trautwein, M.D., and S. Weidmann, M.D.)

*VI. Genesis of the U Wave, *E. Lepeschkin, M.D.*, (With comments by E. Bozler, M.D., and L. Nahum, M.D.)

VII. Instantaneous Equipotential Distribution on the Body Surface during Moments in the U Wave in Normal Subjects and in Patients with Cardiac Pathology, *L. H. Nahum, M.D., and S. Nuland, M.D.* (With comments by E. Lepeschkin, M.D.)

VIII. The U Wave in Esophageal Electrocardiograms, *Jan Nyboer, M.D., Sc.D.* (With comments by E. Lepeschkin, M.D.)

IX. The Form of the Normal U Wave, *E. Lepeschkin, M.D.*

X. The Duration of the U Wave in Relation to the Heart Rate and the Mechanical Events of the Cardiac Cycle, *E. Lepeschkin, M.D., and B. Surawicz, M.D.*

*XI. Coupling Intervals of Ventricular Extrasystoles in Relation to the Heart Rate, the U Wave, and the Supernormal Phase of Excitability, *M. B. Rosenbaum, M.D., and E. Lepeschkin, M.D.*

*XII. Polarity and Amplitude of the U Wave of the Electrocardiogram in Relation to that of the T Wave, *Borys Surawicz, M.D.*,

II. Various Types of Fusion Between T and U Waves

By MAX HOLZMANN, M.D.

THE study of the U wave and of its clinical significance depends upon its accurate recognition. Accurate identification of the U wave is also needed for a correct determination of the Q-T duration. This identification is sometimes difficult because of superposition and fusion of the T and U waves. The term "superposition" is applied to patterns in which these waves are only partially merged and a notch is present by which the 2 components can be separated. The term "fusion" implies uniform monophasic or diphasic waves that show no landmarks for the differentiation of their components. Although the partially merged T and U waves have also frequently been misinterpreted as T waves, the greatest difficulty lies in the recognition of TU-fusion patterns.

The appearance of TU-fusion waves depends on certain peculiarities of the component waves, which are not the same for monophasic and diphasic patterns. The conditions under which upright TU-fusion waves appear will be investigated first. On analysis of such patterns, 3 types of monophasic TU-fusion waves can be differentiated.[1]

Figure 1*A* demonstrates sinus arrhythmia after mild exercise in a 29-year-old man with neurocirculatory dystonia. At the beginning and at the end of the tracing the U waves are rather high, their summits are drawn near the T waves (T-aU = 0.05 sec.), and the junctions between T and U are elevated. These are typical superposition TU waves. In the middle part of the tracing, on the other hand, during a phase of bradycardia, there is a uniform broad and high wave in lead II. The apex of this wave is situated between the summits of the T and U waves in lead I, where it can be distinguished well. To understand the mechanism of fusion of the 2 waves in lead II, we must consider that the apex of the T wave occurs later due to the slowing of the rate, that the U wave becomes higher for the same reason, and that the apex of the U wave remains fixed or is even drawn nearer to the T wave. Consideration of lead I shows that both T and U are involved in the formation of the fusion wave in lead II.

In figure 1*B* the 2 forms of merging of T and U in this case are analyzed. For the double TU wave (complex 2 of lead II) we must assume that the U wave begins before the T wave ends but after the apex of T. The fusion TU wave (complex 4 of lead II), on the other hand, is determined by the U wave beginning not only before the end of the T wave, but also at or before the apex of T. This fusion pattern with a new and higher summit may be called a "TU-fusion wave with a summation apex" or with "equidominant T and U components," in which the T and U components hardly differ in their amplitude and the U-wave upstroke is steeper than the T-wave downstroke.

Figure 2*A* shows a normal resting electrocardiogram of a 44-year-old man with silicosis. The Q-T duration, the interval between Q and the second heart sound, and the relation between the summits of U and T are normal. Immediately after ascending 6 flights of stairs (fig. 2*B*) the Q-T interval in the leads I-III and the interval from Q to the second heart sound are shortened more than would be expected at the resulting heart rate. In the precordial leads, however, a higher upright wave appears, the termination of which produces an interval about as long as the expected Q-U interval. Therefore we must assume that this wave is a TU-fusion wave. This mechanism becomes obvious in succeeding tracings. One half minute later (*B2*) a notch appears that coincides with the notch separating the U wave from the T wave in the limb leads. The emerging U wave is much lower than the T wave. The interval T-aU as well as the interval Q-U appear to be shortened.

Figure 3 from the same case shows in dotted lines the resting pattern in leads II and V_3, with the second heart sound designated by an arrow, and in solid lines the findings after exercise. The tall waves in V_3 cannot be ex-

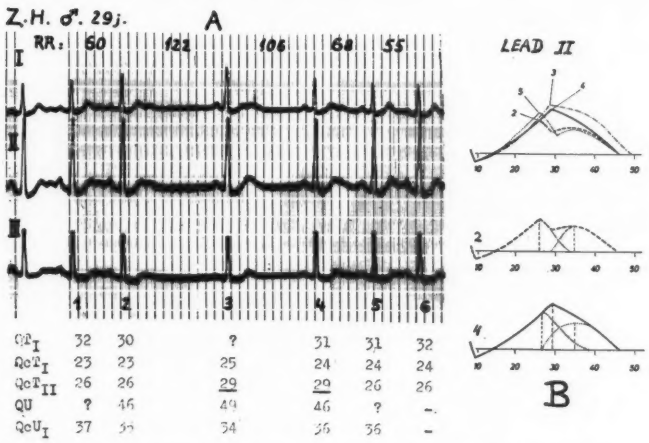

FIG. 1. Analysis (*B*) of an example (*A*) of superposition (complex 2) and complete fusion (complex 4) of equidominant T and U waves during respiratory arrhythmia. In this and in the following figures, QT indicates the distance (in hundredths of a second) from the beginning of QRS to the end of T (Q-T), QcT is a similar distance to the apex or "culmination" of T (Q-aT), QU is the distance to the end of U (Q-U), and QcU is the distance to the apex of U (Q-aU). The time lines in all figures are 0.02 and 0.10 sec. apart.

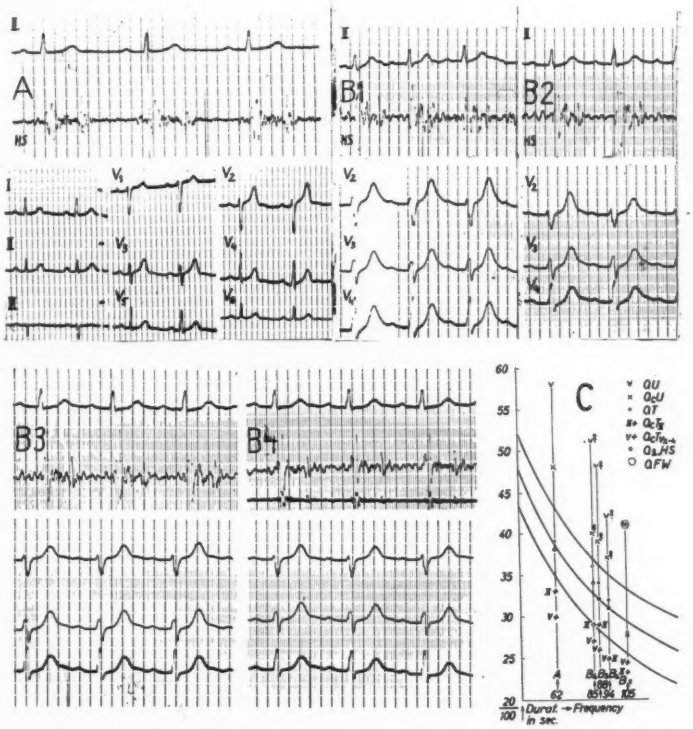

FIG. 2. Development and regression of TU fusion with predominancl of T. *A*. At rest. *B1–B4*. After exercise. *C*. Comparison of the values, as in figure 1, plotted against the heart rate ("frequency"), with the normal average and extreme values of Q-T (3 curved lines). Q2HS = distance to the beginning of the second heart sound; QFW = distance to the end of fusion wave.

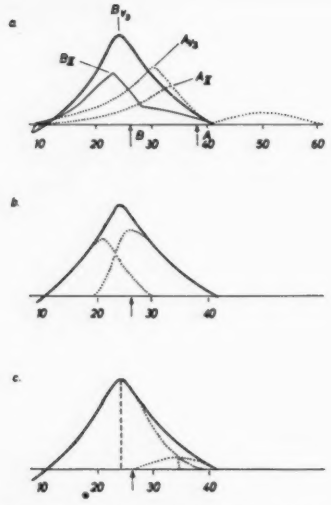

FIG. 3. *a*. Comparison of the TU-fusion waves in leads II and V_3 in tracings *A* and *B1* of figure 2. *b*. Trial analysis of the fusion wave in V_1 as an equidominant fusion wave. *c*. Analysis of the same wave as a fusion wave with predominant T.

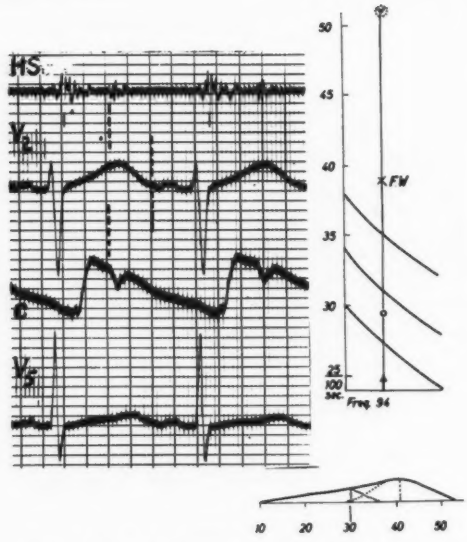

FIG. 4. Analysis of TU-fusion waves with predominance of U in lead V_2 during the effect of insulin. On the right of the electrocardiogram, the intervals are compared with the normal Q-T duration for the heart rate (*Freq.*) as explained in figure 1.

plained as the result of fusion of T and U waves of similar height (fig. 3*b*), as was done in the preceding case. This explanation is contradicted by two facts: the U wave would then begin before the second heart sound, which is not in agreement with our experience; and the U wave, which can be seen in some of the tracings, is much lower than the T wave. This fusion wave must therefore be attributed to superposition of a high T and a small U wave. Considering the onset of the second heart sound, one must suppose that the U wave begins after the peak of the T wave (fig. 3*c*). The descending branch of the T wave crosses the apex or the descending limb of the U wave, and the apex of this fusion wave is identical with the peak of the T wave. This type can be called a "TU-fusion wave with predominance of T." From a similar analysis of the limb leads we must conclude that the Q-T interval is much longer in precordial leads V_2 and V_3 than in the limb leads, but that the Q-T interval is not so prolonged as it would seem if the fusion wave were considered simply a T wave. We can conclude that there may be a difference in length of the Q-T interval between the sagittal and the frontal planes. Such an abnormal Q-T prolongation in the sagittal leads is not surprising, since, in our case, it can be attributed to the effect on the right ventricle of impairment of the pulmonary circulation.

Figure 4 was obtained from a patient in diabetic coma under insulin treatment.[2] The broad upright waves seem to be T waves but last much longer than the interval from the Q to the second heart sound, the interval from Q to the carotid notch, or the Q-T interval predicted according to the heart rate. An almost invisible notch in lead V_5 strongly suggests that in this case also we are dealing with TU-fusion waves. The summit of this broad wave occurs very late. If we assume that the U wave does not begin before the second heart sound but begins with the apex of T, that the ascending branch of U is steeper than the descending branch of T (this is plausible since the U wave is much higher than the T wave), and that the T wave ends before the apex of U (see lower diagram of figure 4), the analysis reveals a new type of TU-fusion wave. It may

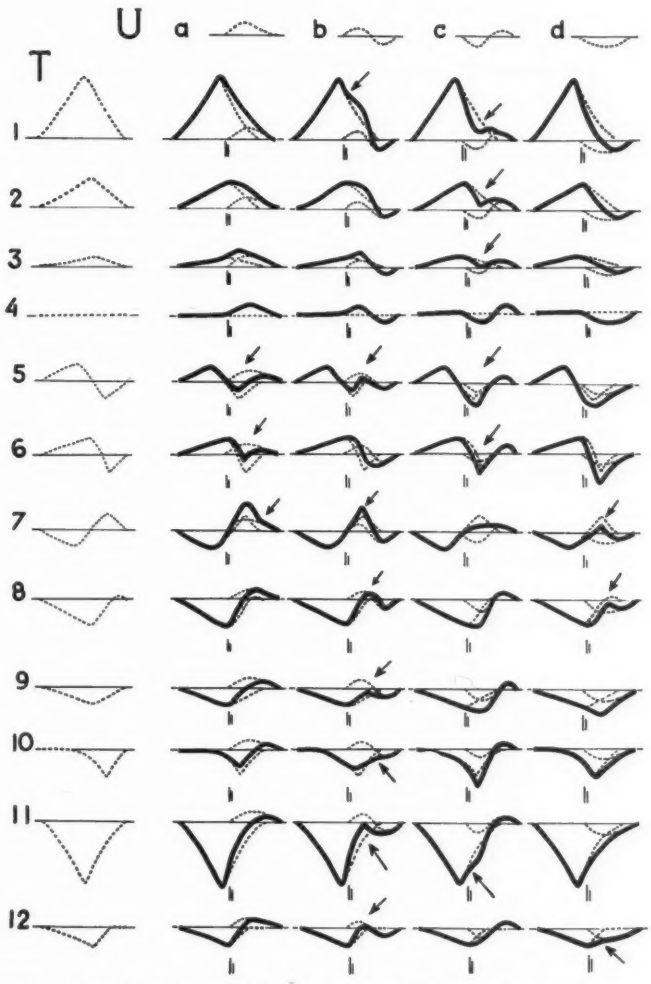

FIG. 5. Patterns caused by superposition or fusion of different types of T waves with different types of U waves.

be called "TU-fusion wave with predominance of U." The apex of this wave is identical with the apex of U. Hypopotassemia is the most frequent condition favoring such a pattern.

Lepeschkin and Surawicz[3] have demonstrated in a very clear manner 16 possible combinations produced by partial merging of upright, diphasic, and inverted T and U waves. Figure 5 shows the 48 theoretical patterns that can result from different degrees and types of merging of T waves of different heights with different forms of U waves. These patterns are constructed on the basis of the assumption that the U wave begins with the second heart sound and with the apex of the T wave. In the case of a marked predominance of T and prolongation of Q-T, the same patterns can appear also if U begins later. When the resulting wave is triphasic or shows a notch, the composition of the wave from 2 separate components is obvious; this is indicated by an arrow. In the first column, (*a*) positive U waves, the TU-fusion waves with a predominant T component appear twice (*1a*, *2a*). The type

with a summation apex appears once (*3a*). The type with a predominant U wave is represented only by the superposition of an isoelectric T wave upon the U wave (*4a–d*). In this case the pattern could be mistaken for a T wave with a prolonged Q-T interval and a long isoelectric S-T segment. The occurrence of the second heart sound before this wave, however, is a valuable aid in the correct interpretation. Unless the patterns are compared with the patterns in other leads, all of the complexes in row *4* could be interpreted as showing flattened T waves followed by U waves.

The superposition of upright T waves and diphasic U waves (fig. 5, *b* and *c*) does not tend to produce uniform smooth fusion waves. In most instances a notch is present between the waves. But there also may appear a diphasic wave with a flat-topped upright component resembling the configuration shown in pattern *2b*. The superposition of an upright T wave upon an inverted U wave (*d*) may produce a plus-minus fusion wave. If T is high, the pattern may be mistaken for a diphasic T wave with a peaked terminal negative component (*1d*). Such examples occur during transient myocardial ischemia with anginal pain. In the 3 upper examples of the last column of figure 5 are conditions that can produce uniform diphasic fusion waves without any overlapping or notching. On the other hand, if T is isoelectric (*4b–d*), the U wave negativity is easily mistaken for T wave negativity. The patterns in row *4* may be called "pseudofusion" waves because there is no T wave component in the respective leads. Only through comparison with simultaneously registered leads that present distinct T waves can one decide whether or not these U waves overlap T or extend into the Q-T interval.

The superposition of diphasic T waves and various types of U waves (fig. 5, rows *5* through *8*) often produces polyphasic patterns that are not difficult to recognize. In some instances, however, diphasic fusion waves may appear. In the case of plus-minus diphasic T waves, a diphasic fusion wave is produced by a superposition of an inverted U wave (*5d*). Such fusion waves can be seen in lead V_2 of figure 6, situated in the transitional zone between the upright and the inverted T waves. Another example (fig. 5, *6b*) is produced by the combination of a diphasic "coronary" T wave together with a plus-minus diphasic U wave. In these cases the typical aspect of the T wave is abolished. In the presence of a minus-plus diphasic T wave a fusion wave may result with the aid of a U wave of the same type (fig. 5, *7c* and *8c*). If the upright component of the T wave is high, the resulting upright deflection is expanded. If T is chiefly directed downward and its upright component very short, the resulting fusion wave becomes a short positive terminal deflection (*8c*). A similar pattern results from superposition of this latter type of T with an upright U wave (fig. 5, *8a*). A great number of the very striking diphasic patterns in hypopotassemia may be due to this kind of superposition because of a high upright U wave component (fig. 7). If the overlapping of T and U is shorter and the U wave lower, there results a pattern similar to that shown in figure 5, *8a* and *8b*, and frequently seen in leads I, V_5, and V_6 in the presence of left ventricular hypertrophy. For practical convenience the typical diphasic pattern with initial negativity (fig. 5, *7c*, *8a*, *8c*) may be compared to the letter S placed on its side or a "recumbent S," the patterns with initial positivity with a "recumbent mirror-image S." The frequent pattern resulting from superposition of a minus-plus T wave having a low upright component with a minus-plus or inverted U wave (fig. 5, *8d*) resembles an "ascending W" in which the second trough of the letter does not descend as low as the first.

With simply inverted T waves, the possibilities for superposition are principally the same as with upright T waves, but in the form of a mirror image. Diphasic fusion waves of the recumbent S type (fig. 5, *9a*, *9c*, *12c*) or broad monophasic negative fusion waves (fig. 5, *9–11d*) can appear in this way. The minus-plus patterns resemble the types shown in figure 5, *7a*, *7c*, *8a* and *8c*, and appear under the same clinical conditions as in the case of diphasic T waves. Uniform diphasic waves may appear when inverted T waves are followed by upright U waves and the terminal branch of T shows the same inclination as the initial branch of

U without overlapping. But this condition seems not to be a frequent one. The uniform downward patterns are mirror images of the patterns produced by upright T waves. They may be found in similar conditions. The type with the very important predominance of a negative T wave in a case of pulmonary embolism was recognized in 1952 and presented with Ramer[4] (fig. 6). This characteristic sign of acute cor pulmonale is confined to precordial

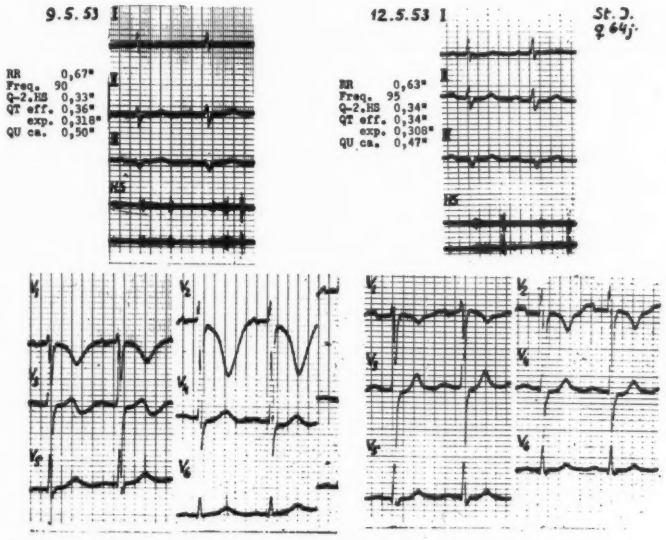

FIG. 6. Deeply inverted U waves causing TU-fusion waves in leads V_1 through V_3 of a case of pulmonary embolism.

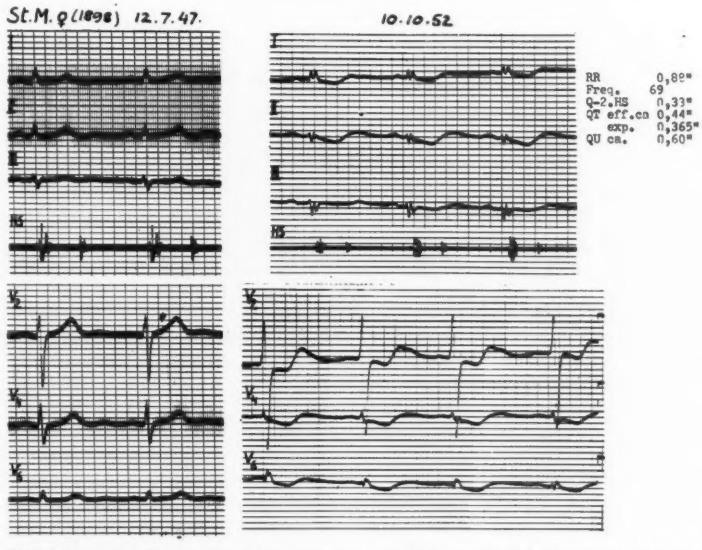

FIG. 7. TU-fusion waves in a case of hypopotassemia. The expected Q-T duration for the heart rate and the actual Q-T duration (*Q-T eff.*), as well as the Q-U duration, are indicated in the upper right hand corner.

leads V_1 through V_4, and is usually best seen in leads V_2 and V_3.

Uniform diphasic waves consisting of T and U waves can appear also without any fusion or overlapping of these waves, if the terminal branch of the T wave is followed immediately by a monophasic U wave of opposite polarity. Such waves may be called "continuation waves."

To recognize TU fusion waves, as well as uniform diphasic TU continuation waves, the following attributes are valuable.[1, 5] 1. Agreement of the interval from Q to the end of the wave with the predicted duration of Q-U interval based on the heart rate. 2. The presence, in other complexes of the same lead, of a notch at the site where the T-U junction is expected according to the heart rate. 3. The recognition of a separation of T and U in other simultaneously recorded leads, at a point where these waves are expected in relation to the heart rate. 4. Observation of separated T and U waves in the same lead in previous or subsequent tracings. 5. Demonstration of the extension of the wave in question beyond the second heart sound by more than 0.04 sec.; if this sound is premature, then beyond the theoretically predicted second sound, according to the heart rate. 6. Demonstration of the components of TU-fusion waves, as Surawicz and Lepeschkin[5] have suggested, by shortening the Q-T interval with calcium chloride or by altering the size of the T and U waves with potassium.

Although the relationship between the second heart sound and the U wave requires further study, it is obvious that the U wave closely follows this sound. In the light of this relationship the circumstances that can produce TU-fusion waves become predictable. These include all factors that lengthen the Q-T interval more than the interval between Q and the second heart sound and that amplify the U waves. These results are brought about by acute overloading of the ventricles and also, as Surawicz and Lepeschkin[5] have pointed out, by the combination of hypocalcemia with hypopotassemia. Another important factor is the so-called energeto-dynamic heart failure studied and developed by Hegglin.[6] Because the second heart sound in this condition appears earlier than predicted in relation of the heart rate or, in other words, because hemodynamic systole is shortened, the U wave also begins earlier. This favors the merging of U and T waves. It must be pointed out, that in this condition prematurity of the second heart sound is essential and the so-called dissociation between the Q-T interval and hemodynamic systole is either an illusion or much smaller than it appears to be. What has been measured in these cases equals actually the Q-U interval.

The presumed close relationship between the second heart sound and the U wave throws some light on the origin of the latter. This relationship fits very well into the concept that the U wave is related to the distention of the ventricular walls during early diastole; however, it does not furnish absolute proof of this concept.

The concepts developed in this paper are essentially in agreement with the statements published by Lepeschkin and Surawicz.[3, 5] In view of these findings it may be necessary for many of us to correct some interpretations of electrocardiograms published in previous papers. To make these concepts familiar to all who may have to deal with the U wave in the future is one of the purposes of this symposium.

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VI. Genesis of the U Wave

By E. Lepeschkin, M.D.

IN THE light of our present knowledge, only 3 explanations appear possible for the U wave: first, this wave is caused by a longer duration of the action potential in some section of the ventricles; second, it is caused by afterpotentials following the action potential proper; and third, it is caused by potentials elicited by the stretching of ventricular muscle during the period of rapid filling. In the following we shall examine how each of these hypotheses fits the actually observed behavior of the U wave.

Einthoven[1] originally explained the U wave as due to persistence of electric activity in some section of the ventricle. Zuckermann and Cabrera[2] considered this section to correspond to the interventricular septum, while the recent work of Furbetta, Bufalari, and Santucci[3] indicated that it corresponds to the papillary muscles, since these authors found in hypothermic dogs that the voltage of U was highest in direct leads from points of the ventricular surface near the origin of these muscles. However, if this hypothesis were correct, direct leads from the papillary muscles should show a duration of the T wave or the monophasic action potential corresponding to the Q-U duration in surface leads; this was never observed. Another possibility is that the region with persistent activity corresponds to the specific conducting fibers of Purkinje. Coraboeuf and co-workers[4] found that in intracellular leads from these fibers the duration of the action potential is about 50 per cent longer than in simultaneous intracellular leads from the nonspecific muscle tissue of the papillary muscles. They considered this difference in duration responsible for the normal direction of the T wave; as the duration of the action potential in the Purkinje fibers corresponds to the Q-U rather than to the Q-T duration, these differences could be well held responsible for the U waves. However, the cross-section of the conducting tissue compared with that of the shortcircuiting plain muscle, and accordingly the voltage produced by its activation in surface leads is very small, and certainly cannot account for the tremendous U waves that may appear in hypopotassemia (see below). Furthermore, a U wave can be seen also in the atrium, which has no conducting system, while negative afterpotentials corresponding in time with the U wave appear also in intracellular leads from the ventricular surface, where no Purkinje fibers are present. However, the greatest difficulty in explaining the U wave as due to persistent excitation in some parts of the ventricle is that this explanation would call for the highest voltage of the U wave immediately after the end of the T wave. In other words, the fact that in most cases there is an isoelectric interval between the T and U waves in all leads cannot be explained by this hypothesis.

The second explanation for the U wave is that it is caused by distention potentials of ventricular muscle, originating during the phase of rapid ventricular filling. Distention of ventricular muscle caused a reversible decrease of 1 to 5 per cent in the value of the injury potential,[5-7] which was attributed to a corresponding decrease in the resting polarization of the cell membrane. However, recent experiments of Dudel and Trautwein[8] showed that the true membrane potential, measured by intracellular electrodes is not influenced even by tensions up to 40 times those developed during systolic contraction of the fiber; further stretching causes an irreversible decrease due to injury. The decrease of the injury current by stretching found earlier is attributed to decrease in the diameter of the muscle fibers, with a resultant greater shortcircuiting effect on the injury potential.[8]

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This work was done during the tenure by Dr. Lepeschkin of an Established Investigatorship of the American Heart Association.

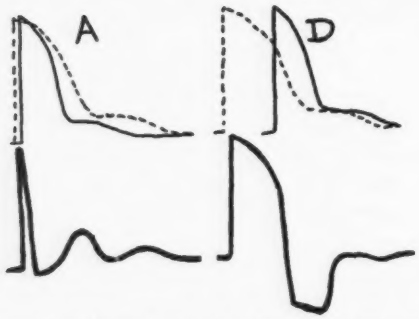

FIG. 1. Schematic construction of the T and U waves as a difference between 2 action potentials with negative afterpotentials. The solid curve represents subepicardial ventricular muscle, which is activated late and has a short action potential. The dotted curve represents subendocardial muscle, which is activated early and has a long action potential; it is an exact copy of the solid curve with a time base extended 1½ times. *A*. Normal conduction. *D*. Delayed conduction, resulting in inversion of T and U.

The best explanation of the U wave is that it corresponds to potential differences produced during the descending limb of a negative afterpotential,* just as the T wave corresponds to similar potential differences produced during the descending limb of the action potential proper. This hypothesis was first made by Nahum and Hoff.[9] Figure 1 illustrates the construction of normal T and U waves based on this assumption; it explains the separation of U from T, as well as the parallelism between the direction of T and U in normal persons and in intraventricular conduction disturbances leading to secondary T wave changes. In this figure, facsimiles have been used of actual intracellular action potentials of the chicken, taken by Fingl, Woodbury, and Hecht[10] since the birds seem to be the only animal species with U waves comparable in size to those of man.[11] In the frog and turtle[12-15] and the dog[8, 15, 16] negative afterpotentials are either absent or do not exceed 3 per cent of the amplitude of the action potential proper; accordingly, these animals show practically no U waves under normal circumstances. Wherever negative afterpotentials have been observed, their position in the cardiac cycle at a given heart rate corresponds perfectly with that of the U wave. Intracellular action potentials have not been registered in the human heart, but in 1 case a negative U wave became transformed into a negative afterpotential when the curve became monophasic due to pressure of the intracardiac electrode.[17]

According to the construction of figure 1 the U wave reflects only the differences in the duration and amplitude of the negative afterpotentials, and not their absolute amplitude; therefore not every change in the U wave would necessarily mean a corresponding change in the afterpotential. However, all factors known to influence the afterpotentials should influence the U wave in the same direction, other things being equal. This is actually the case for all factors studied so far. The negative afterpotential in nerve was attributed[18] to persistence of slight depolarization of the cell membrane after the end of the action potential proper due to the potassium ions that have left the cell during repolarization[19] and are only slowly removed from the cell surface partly by diffusion, partly by active reabsorption into the cell. The descending branch of the action potential of the heart, which corresponds to the T wave of the electrocardiogram, is very probably caused by exit of potassium from the cell, as in the case of nerve.[20, 21] Such an exit during the T wave was actually observed by Wilde and co-workers[22] by means of tracer studies. It is therefore probable that the afterpotentials of heart muscle are also caused by an accumulation of potassium ions that have left the cell during the T wave.[23, 25] If the external potassium is high, less potassium can be expected to leave the cell and more will be reabsorbed during diastole; the negative afterpotentials can therefore be expected to become smaller. Decrease of the extracellular potassium can be expected to have the opposite effect. In agreement with this view, negative afterpotentials of the frog heart,[12] as well as U waves in human beings,[24] decrease regularly

*These afterpotentials were called "negative," since they indicate relative negativity of the cell surface; at the same time they indicate relative positivity of the cell interior, so that they are positive in the intracellular curve of figure 1.

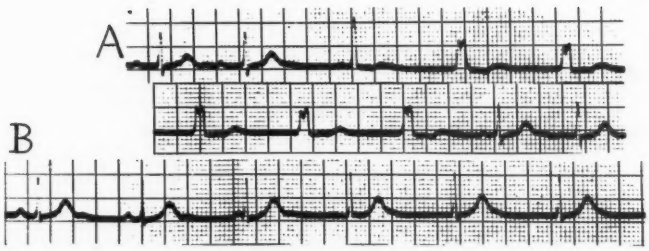

FIG. 2 *A*. Lead I of a young man with tonsillitis, showing ventricular parasystole with fusion beats. The 2 strips are continuous. The beats with wide QRS show inversion of T but little change of U. *B*. Lead II of an apparently healthy young woman, showing partial fusion of T and U during the appearance of an A-V nodal rhythm, without change of heart rate or the configuration of QRS and T.

with increasing external potassium concentration. On the other hand, low serum potassium is characterized by an elevation of the U wave[24, 25] greater than that caused by any other single factor; even dogs and rabbits, which ordinarily show no U waves, develop them when the heart is perfused with solutions low in potassium[26] or when hypopotassemia develops during the course of alkalosis.[27, 28]

Epinephrine causes elevation of both the negative afterpotentials of the frog heart[12] and of the U wave.[29, 30] This effect is probably related to the increased potassium loss from the heart after epinephrine[31, 32]; the elevation of the U wave also can be prevented by administration of potassium.[23] The increase of the negative afterpotentials of the frog heart[12,33] and of the U wave[34] after veratrine can be attributed to decreased velocity of reabsorption of potassium, as in the case of nerve,[18] since it can be prevented by high external potassium[33] which would be expected to increase the rate of reabsorption. The increased amplitude of the negative afterpotential of the frog[12] and of U waves in human beings[35] under the influence of digitalis also can be attributed to inhibition of the diastolic reabsorption of potassium, which is considered responsible for its positive inotropic effect.[36] Calcium has a similar effect on the negative afterpotentials[12] as well as the U wave.[35]

Very significant for the interpretation of the U wave is the finding of Dudel and Trautwein,[8] that stretching causes an increase of the negative afterpotentials of cardiac muscle up to 20 per cent of the height of the action potential. Accordingly, the negative afterpotentials would be expected to be highest in parts of the ventricle subjected to greatest stretch. As a result the U wave tends to show negative polarity in unipolar leads facing these parts and positive polarity in leads facing parts of the ventricle subjected to least stretch and, in addition, tends to have the same direction as the T wave expected from the construction of figure 1. This explanation would fit the observation of Furbetta and co-workers[3] that the U waves are highest on the ventricular surface opposite the insertion of the papillary muscles, for these muscles must bear the entire systolic ventricular pressure that is exerted on the atrioventricular valves. It would also explain the fact that the maximal voltage of U in precordial leads of normal adults is situated slightly to the right of the maximal T wave voltage, and that in children T may be inverted in leads V_1 through V_4 while U is always upright in these leads. It may also account for the fact that in some cases of transient bundle-branch block or extrasystoles, T may become negative while U remains almost unchanged (fig. 2*A*), and that primary changes of T usually do not affect the U wave. That an A-V nodal rhythm may cause the U wave to become taller and begin earlier without any change of heart rate, QRS, or T (fig. 2*B*) can also be explained only by assuming that absence of atrial contraction preceding ventricular systole increases the early diastolic ventricular filling pressure and thus influences the afterpotentials.

Segers[12] found that under conditions of in-

creased intraventricular pressure or in old, anoxic preparations, the negative afterpotentials can be transformed into diphasic and finally into positive afterpotentials; these changes occur at a time when the action potential proper is scarcely modified. A similar mechanism could be held responsible for the primary U wave changes resulting in "isolated inverted U waves" in the presence of upright T waves, which sometimes appear in conditions leading to left ventricular hypertrophy and, less commonly, in myocardial ischemia. Another possibility is that these U waves are caused by an accentuation of negative afterpotentials in the thin ventricular apex, which would be stretched first in beginning dilatation of the ventricle. Only the registration of intracellular or monophasic action potentials in persons with isolated inverted U waves can decide between these possibilities.

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XI. Coupling Intervals of Ventricular Extrasystoles in Relation to the Heart Rate, the U Wave, and the Supernormal Phase of Excitability

By EUGENE LEPESCHKIN, M.D., AND MAURICIO B. ROSENBAUM, M.D.

ACCORDING to our present state of knowledge it seems very probable that the U wave of the electrocardiogram is caused by the summation of afterpotentials in cardiac muscle, and that the normal positive U waves are caused by the summation of negative afterpotentials. Since these potentials are accompanied in nerve or muscle by a temporary reduction of the threshold of excitability (supernormal phase of excitability), it follows that the U wave must correspond to this supernormal phase, as was first suggested by Nahum and Hoff,[1] who observed that coupled ventricular extrasystoles usually occur during the writing of the U wave. In the present paper it was intended to test this concept by determining whether or not factors that alter the amplitude or time of appearance of the U wave have a corresponding effect on the incidence or time of appearance of ventricular extrasystoles. Furthermore, it was of interest to know whether persons showing primary U-wave inversion, which was attributed to the appearance of positive afterpotentials corresponding to a phase of subnormal excitability, show a different incidence or timing of extrasystoles than persons with normal U waves.

One of the most important factors that influence the time of appearance of the U wave is the heart rate. Therefore it was important to determine whether in the regularly beating heart the coupling interval of ventricular extrasystoles decreases with increasing heart rate in the same way as does the duration of the Q-U interval. In figure 11 of Nahum and Hoff's paper[1] it can be seen that, in 10 patients showing an R-R interval of 0.50 sec. and an average Q-T interval of 0.36 sec., the coupling interval of extrasystoles (Q-E interval) ranged between 0.29 and 0.42 sec.; in 67 patients with R-R intervals of 0.60 to 0.80 sec. and an average Q-T of 0.30 to 0.40 sec., the Q-E interval ranged between 0.40 and 0.65 sec.; while in 11 cases with an R-R interval about 1.00 sec. and an average Q-T interval of 0.36 sec. the Q-E intervals ranged between 0.65 and 1.00 sec. Only the extrasystoles of the second group were said to appear during the U wave, whereas those of the first group appeared while the descending branch of T was being written and those of the third group appeared during and after the inscription of the P wave. Koulumies and co-workers[2] stated that of 500 cases with prominent U waves extrasystoles were present in 27, appearing during the U wave in 25 and during the P wave in 2 cases. Zuckermann and Estandia[3] stated that in 300 instances mechanical stimulation of the septal region of the ventricle in dogs always caused extrasystoles, which appeared late (during or after the P wave), while stimulation of the free walls of the ventricle led to extrasystoles appearing during or immediately after the inscription of the T wave, where a U wave would have been found, if it were present in dogs. In their figure 7 the authors showed that in human subjects about 70 ventricular extrasystoles appeared synchronously with the U wave, while 7 appeared after it and during the P wave or P-R segment. These latter extrasystoles, which the authors considered to originate in the ventricular septum in analogy to the findings in dogs, were characterized by an initial slurring of the QRS, which was upright in the left as well as the right precordial

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This work was done during the tenure by Dr. Lepeschkin of an Established Investigatorship of the American Heart Association.

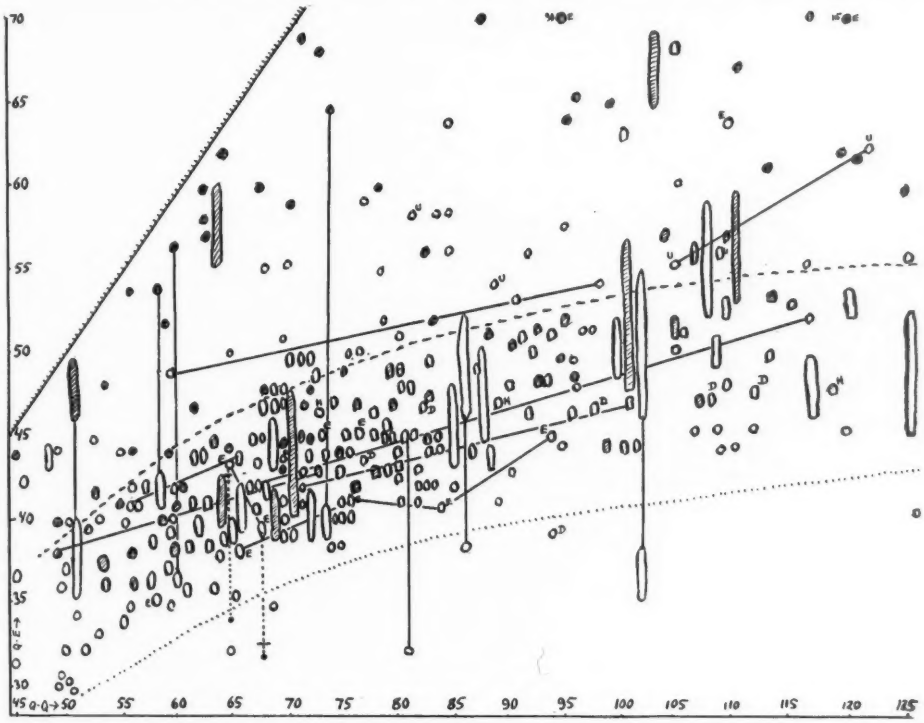

FIG. 1. Relation of the coupling intervals of ventricular extrasystoles (Q-E, on ordinate) to the preceding pulse interval (Q-Q, on abscissa), in 250 cases (represented by circles and ovals). Dotted curve, average Q-aU intervals; dashed curve, average Q-T interval for each pulse interval. All values are in hundredths of a second.

leads. The initial slurring was also present in the septal extrasystoles produced experimentally in dogs.

In order to study the coupling intervals of ventricular extrasystoles in relation to their configuration as well as to the heart rate, the coupling intervals (Q-E) of 250 personal cases, in which at least 3 ventricular extrasystoles were registered, were plotted in figure 1 in relation to the average R-R interval of each case. Since the number of cases showing extrasystoles at ventricular rates exceeding 100 was too small to warrant any definite conclusions, 30 additional measurements were made on electrocardiograms of such cases published in the paper of Berliner and Huppert.[4] Each case is represented by an oval that contains all the measured Q-E intervals. In addition to these 250 cases, very long tracings, containing at least 20 extrasystoles, were taken in 20 cases in a single lead; these correspond to the very long ovals in figure 1. If the coupling intervals fell into 2 or more distinct groups, these groups are indicated by ovals connected by continuous vertical lines. If the coupling intervals were studied at 2 different heart rates in the same case, the ovals corresponding to these intervals are connected by continuous diagonal lines. The average Q-T and Q-aU intervals for each heart rate are indicated by dashed or dotted curves respectively. If in a given case these intervals are significantly different from the average, they are indicated by a dash or dot, respectively, connected to the corresponding Q-E interval by an interrupted vertical line. The diagonal straight line at the upper left hand corner indicates the natural limit of Q-E for each Q-Q interval, that is, the value of Q-E at which it is equal to Q-Q. Extrasystoles that

have a coupling interval exceeding this value will not appear at all at a given heart rate.

An attempt was made to estimate the speed of the initial component of ventricular extrasystoles by determining the maximum voltage developed in any lead during the first 0.04 sec. of the QRS complex; if this voltage did not exceed 2 mm., the beginning of the extrasystole was said to be slow; the ovals corresponding to such extrasystoles in figure 1 were shaded. Extrasystoles appearing in persons showing primary (isolated) inversion of the U wave were designated by the letter "U" next to the corresponding ovals. Extrasystoles appearing in persons treated with digitalis and showing a configuration of T and S-T typical for the digitalis effect were marked with the letter *D*, those appearing under the influence of epinephrine were marked with the letter *E*, and those appearing in hypopotassemia were marked with the letter *H* next to the corresponding ovals.

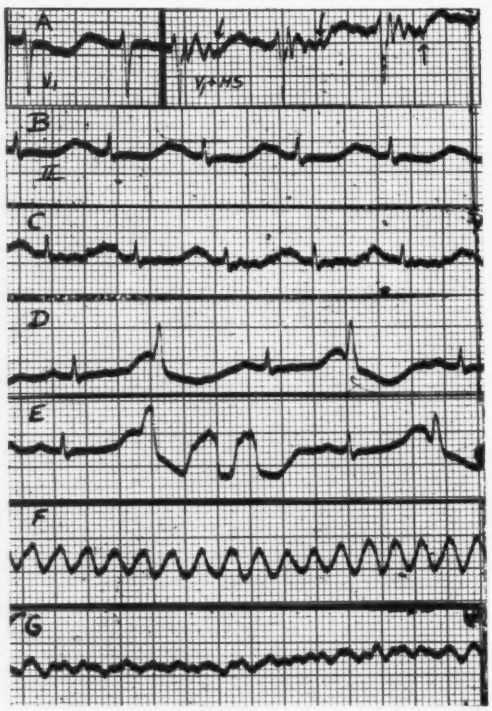

FIG. 2. *A*. Lead V_2, with the heart sounds superimposed upon it in the second half, in a 68-year-old woman with severe vomiting and diarrhea. The tall late upright waves that appear as diphasic T waves are in reality tall U waves, since their apex appears very late, long after the second heart sound (indicated by arrows). *B*. Lead II in the same case. The serum potassium at this time was 2.5 mEq./L., the serum sodium 110 mEq./L. *C*. Lead II after infusion of potassium in dextrose solution (the amount of potassium evidently was not sufficient to counteract the potassium fixation caused by dextrose). The U waves are now taller than the R waves. *D*. The U waves are even taller, and ventricular extrasystoles appear at their summits. *E*. The ventricular extrasystoles are followed by short runs of ventricular tachycardia. The infusion was discontinued at this point. *F*. Ventricular flutter. *G*. Ventricular fibrillation. These electrocardiograms were registered by D. Lareau, M.D. and interpreted by B. Surawicz, M.D.

Figure 1 shows first of all that the average value of the coupling intervals increased with falling heart rate, and that this increase approximately paralleled that of the Q-aU interval; the great majority of the single values seem to be situated between Q-T and a curve about 0.5 sec. above the Q-aU curve. In all cases where the same type of ventricular extrasystoles appeared at widely different heart rates (circles connected by diagonal lines) the coupling intervals were shorter at the higher rate (fig. 1). In 5 cases in which extrasystoles appeared in groups of 2 or more, the coupling interval was always shorter in the second extrasystole, corresponding to the shorter pause preceding the beat to which the extrasystole was coupled; this is a common finding.[5] In such cases it seemed that the extrasystoles originated at the same point on the U waves regardless of their coupling intervals.

In the 20 cases in which a very large number of extrasystoles was registered in the same lead, when the extrasystoles appeared in bigeminal rhythm or regularly after every 2 or 3 normal beats, the coupling intervals remained constant within 0.02 sec. However, when the extrasystoles occurred irregularly, the coupling intervals varied on the average 0.04 sec. and in some cases up to 0.11 sec. In all these cases the extrasystolic beats were truly coupled to the preceding normal beats, for they did not appear in the latter half of the diastolic period. In 4 cases, however, 2 groups of coupling intervals were found; the intervals

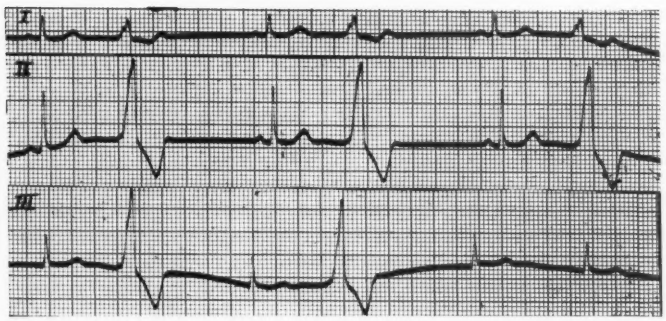

FIG. 3. Ventricular extrasystoles with long coupling intervals and very slow initial slope in all leads, appearing after the end of U during infusion of norepinephrine in a normal young woman.

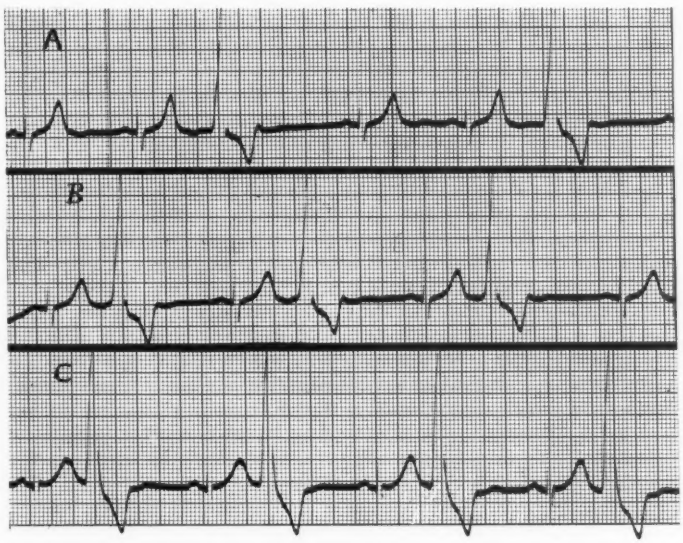

FIG. 4. *A*. Ventricular extrasystoles with longer than average coupling intervals in a case of mild hypertension with isolated diphasic U waves. *B*. Shortening of the coupling intervals when the pause preceding the beat followed by the extrasystole lengthens due to bigeminal rhythm. *C*. Further shortening of the coupling intervals with acceleration of the heart in the upright position, in which the U waves become positive. The U waves of the extrasystoles are also inverted in the first tracing, diphasic in the second, and upright in the third.

within each group did not vary more than 0.11 sec., and in all cases the configuration of the extrasystoles in these 2 groups was different. In all these cases with slightly variable coupling intervals measurement of the interextrasystolic intervals showed that a parasystolic rhythm could be held responsible for them only under the assumption that the rate of this rhythm varied more than 10 per cent. The maximal variation of the coupling intervals in a given case therefore exceeds the 0.04 quoted by Scherf and Schott.[5]

In 34 cases (about 13 per cent of the series) the extrasystoles appeared very late in diastole, long after the apex of the U wave; these extrasystoles seemed to be distributed evenly throughout the diastole without relation to the heart rate. In 28 of these (fig. 3) the extrasystoles began with a slow initial component, while of the 185 remaining cases in which the

slope of the initial component was determined, only 65 showed a slow slope. In all 4 cases that showed both the late and the early type of extrasystoles, the former always had a slow initial component while in the latter this component was rapid. In figure 127 of Scherf and Schott,[5] where the coupling intervals were unusually long (1.12 sec.), the initial slope was also relatively slow. Thus the observations of Zuckermann,[3] mentioned in the introduction, were confirmed in general. However, in the 35 cases where extrasystoles were registered in all precordial leads, there was no apparent relation between the coupling intervals and the direction of QRS in these leads.

In the cases where ventricular extrasystoles appeared after digitalis (*D*) or in hypopotassemia (*H*) the coupling intervals did not differ appreciably from the usual values at the same heart rate, although in the case of digitalis Q-T was definitely shorter; in both groups the apex of U appeared at the usual time. However, in extrasystoles appearing during administration of epinephrine (*E*) the coupling intervals were usually either considerably outside of the usual range for the heart rate, or on the lower limit of this range; in 2 cases it could be seen that the average coupling intervals decreased parallel to a decrease in the Q-aU interval while Q-T retained its normal relation to the heart rate (fig. 4). As for extrasystoles in the presence of isolated inverted or diphasic U waves, these could be observed in only 4 cases. In all of these the coupling intervals were on the upper border of the usual values for the heart rate; in 1 case (fig. 2) these intervals became average in the upright position, when the heart rate increased and the U wave became completely positive.

In 7 cases the coupling of ventricular extrasystoles was shorter than the average Q-T interval; in all these cases the extrasystoles began before the end of the T wave. Four of these had fresh myocardial infarction while 3 had advanced cardiac failure incident to hypertensive heart disease (fig. 1); 2 of the latter group were receiving digitalis but did not show the typical digitalis pattern in the electrocardiogram. In all 7 cases the extrasystoles had a rapid initial component; in 3 there were other ventricular extrasystoles of a different configuration that showed coupling intervals of an average duration.

Discussion

There are 2 groups of explanations for coupled extrasystoles. According to the re-entry hypothesis,[8] some section of the conducting system may have a prolonged refractory period and accordingly not be excited when first reached by the normal impulse; when the same impulse reaches it shortly afterwards by another pathway, it then excites the region, since its refractory period would be over. Owing to slow velocity of conduction within it, this region would not re-excite the rest of the ventricle until after a period corresponding to the coupling interval of the extrasystoles. According to this explanation, the extrasystole would occur only if the normal beat happens to occur exactly at the end of the prolonged refractory period; appearance of coupled extrasystoles at widely varying heart rates in the same person would not be explained by it. Furthermore, according to any hypothesis that attributes the coupling interval to a greatly prolonged focal conduction, this interval would be expected to show a marked increase with rising heart rate; actually this interval in general decreases with rising rate (fig. 1). The re-entry hypothesis has not been proved, and numerous objections have been advanced against it.[5]

An explanation which has been proved to apply even to single cells by means of intracellular electrodes[6, 7] is that coupled extrasystoles are caused by a temporary increase in excitability following the relative refractory phase (supernormal phase of excitability). Theoretically, there are 2 possibilities for the appearance of extrasystoles due to the supernormal phase. In the first, a constant stimulus (a constant slight depolarization of the cell membrane) is present in some circumscribed region of the myocardium. If this stimulus is very weak, it will excite only at the peak of the supernormal phase of excitability; if it is stronger it will excite earlier, at the beginning of this phase. Finally, if the stimulus is very strong, it will excite at the end of the absolute refractory phase, and the coupling intervals will be extremely short, the extrasystoles ap-

pearing very soon after the apex of the T wave. In any case the coupling intervals should be constant.

The second possibility is that the stimulus is not constant but arises in a parasystolic center that is so weak that it can excite the muscle surrounding it only during the supernormal phase. This possibility was mentioned by Schaefer.[9] In this case, if the rhythmic stimulus is weak, it will cause extrasystoles only occasionally, when it occurs at the height of the supernormal phase, and the coupling intervals will be approximately the same. If the stimulus is stronger it will excite also at the beginning and at the end of the supernormal phase; the extrasystoles will be more abundant and their coupling intervals will vary within the limits of 0.10 to 0.25 sec. (which is the duration of the supernormal phase).

In both possibilities discussed above the duration of the coupling intervals is complicated by the fact that there may be a considerable conduction delay ("perifocal block") between the site of origin of the extrasystoles and the neighboring myocardium. The magnitude of this delay may depend on the pause between the regular heart beats if this perifocal tissue is excited also by the normal beats, or it may depend on the pause between extrasystoles if it shows protective block from the normal beats and is excited only by the extrasystoles.[8] We can, therefore, reach the conclusion that, while in general the coupling of extrasystoles decreases with rising heart rate due to earlier occurrence of the supernormal phase, a perifocal conduction delay may counteract or even reverse this tendency in a given case.[9] The great variability of the coupling intervals found in some of our cases (long ovals in fig. 1) can be attributed to this factor, while in others it could have been due to a parasystolic nature of the stimulus.

The supernormal phase of excitability in the frog heart was found to correspond to the negative afterpotentials, and was attributed, as in nerve, to partial depolarization of the cell membrane by these afterpotentials.[10] This depolarization reduces the strength of stimulus needed to reduce the membrane potential to critical levels, at which the sodium permeability exceeds the potassium permeability, initiating a spontaneous action potential.[6, 7] If the normal U wave is caused by negative afterpotentials, then a supernormal phase should be present whenever definite U waves can be seen. Actually, a supernormal phase was found in all cats and monkeys under barbiturate anesthesia with natural respiration[1, 11] but only occasionally or not at all in cats and dogs under artificial respiration.[11-16] In studies with greater precision of measurement a supernormal phase was frequent, but it corresponded to a decrease of threshold of only 5 to 15 per cent.[6] The reason for this difference may be that the depressed respiration due to barbiturates and a partly opened chest probably leads to acidosis, while artificial respiration tends to produce hyperventilation and alkalosis; the supernormal phase was found to be especially marked in an acid reaction[17-19] or in "fatigued" hearts[20] or excised myocardial strips,[10, 21, 22] where hypoxia and acidosis are probable. The only occasional occurrence of the supernormal phase in the normal dog heart is not in conflict with the concept concerning the genesis of the U wave mentioned above, since dogs normally show no recognizable U waves. Studies on the cardiac excitability in man or in other animals having tall U waves have not been carried out. On the other hand, the absence of a U wave does not preclude the appearance of extrasystoles due to a supernormal phase, since negative afterpotentials could be present in the very small localized region of the myocardium that gives rise to extrasystoles, without appearing in the surface electrocardiogram. A local increase in acidity favoring the appearance of a supernormal phase can very well be the result of focal coronary sclerosis or myocarditis, which is responsible for extrasystoles in most cases. The fact that the coupling intervals of ventricular extrasystoles were influenced by epinephrine, digitalis, and especially by changes in the heart rate in approximately the same way as the Q-aU interval, is in keeping with the assumption that these extrasystoles are caused by the supernormal phase of excitability.

The great majority of ventricular extrasystoles studied by us began during the period extending from 0.03 sec. after the end of the T wave or the beginning of the U wave to about

0.05 sec. after the apex of the U wave. If the beginning of the U wave corresponds to the plateau of the negative afterpotential while the apex of the U wave corresponds to its descending branch, this observation would indicate that the extrasystoles begin during the ascending branch or the apex of the supernormal phase of excitability, if a perifocal conduction interval of 0.01 to 0.05 sec. is assumed. The extrasystoles with fairly constant coupling intervals can then be interpreted as being elicited by a constant stimulus while those with variable coupling intervals might be caused by a parasystolic stimulus. That no common denominator could be found for the interextrasystolic intervals in our cases would not exclude a parasystolic stimulus, since the rate of such a stimulus, as well as the perifocal conduction time, can vary considerably.

It was mentioned that cases with isolated diphasic (±) U waves showed coupling intervals exceeding the average intervals found at the particular heart rate in the few cases studied. If this observation should be confirmed on a larger series, it would definitely be in favor of this form of U waves being due to the appearance of diphasic (− +) afterpotentials, since then the supernormal phase, which would correspond to the negative phase of such afterpotentials, would be expected to begin late.

In the light of our concept concerning the genesis of the U waves, we would expect that all factors that increase the amplitude of the U waves would also facilitate the appearance of coupled extrasystoles. In the amphibian heart, there seems to be an exact parallelism between the amplitude of the negative afterpotential, the supernormal phase, and the appearance of these extrasystoles.[10] In the mammalian heart, this same parallelism is present following the administration of epinephrine, calcium, and digitalis; the prevalent type of extrasystoles elicited by these drugs is the coupled one, with the ectopic beat beginning at the peak of the elevated U waves. In hypopotassemia, where elevation of U waves is one of the most constant signs, ectopic beats are common, but usually are of supraventricular origin.[23] However, when they do originate in the ventricles, they always appear at the summit of the U waves.[24] Figure 3 shows the development of coupled ventricular extrasystoles parallel to increase in the amplitude of the U wave in a case of hypopotassemia; during the U wave of these extrasystoles other extrasystoles appeared, and this evidently led to re-entry and ventricular flutter and fibrillation. The same sequence was observed recently in rabbit hearts perfused with a low potassium solution.[25] On the other hand, potassium decreases the U waves and the afterpotentials, and suppresses all coupled extrasystoles.[23]

In acidosis, which is known to elevate the U waves, a supernormal phase was found to appear in the mammalian heart, and this was accompanied by the appearance of ventricular extrasystoles with coupling intervals corresponding to the duration of this phase.[19] Slowing of the heart rate, which tends to elevate the U waves, also favors the appearance of coupled rhythms; we have seen this event in many cases of atrial fibrillation treated with digitalis, where coupled extrasystoles were precipitated only by ventricular complexes appearing after long pauses. This observation was made previously.[5, 8]

The only discrepancy between the amplitude of the U waves and the effect on excitability is the suppression of coupled extrasystoles by quinidine in spite of its elevating effect on the U waves; the explanation of this peculiarity could be that the threshold of excitability is raised to such a degree by quinidine that even the presence of an increased supernormal phase still does not lower it sufficiently for excitation by the ectopic stimulus.

The few extrasystoles with very short coupling intervals found in figure 1 could be explained by the presence of a very intense continuous stimulus, which excites at the end of the absolute refractory phase and before the end of the T wave. In the case of acute myocardial infarction or congestive heart failure, localized partial depolarization of the muscle membrane can act as such a stimulus.[26] All patients exhibiting such short coupling intervals were in grave condition. This association was also found by Smirk,[27] although in some of his cases R waves of extrasystoles

interrupted T waves not because the coupling intervals were short, but because the Q-T intervals were prolonged.

In the extrasystoles that appeared after the U wave and therefore showed long coupling intervals in figure 1, a relation between these intervals and the heart rate was present only inasmuch as these extrasystoles could not appear at fast heart rates, when the Q-Q interval was shorter than the coupling interval; beyond this minimal Q-Q interval there seems to be no relation to the heart rate. The best explanation for these extrasystoles is that they are caused by automatic stimulus formation, that is, that they represent escape beats with a short preautomatic pause. Such automatic stimulus formation is the result of gradual membrane depolarization during diastole, culminating in a prepotential of rapidly increasing amplitude; when this prepotential reaches the critical membrane potential, the membrane is depolarized and a conducted action potential results.[6, 7] The fact that nearly all extrasystoles appearing late in diastole began with a slow initial component gives support to this interpretation.

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XII. Polarity and Amplitude of the U Wave of the Electrocardiogram in Relation to that of the T Wave

By Borys Surawicz, M.D., Robert L. Kemp, M.D., and Samuel Bellet, M.D.

MANY authorities regard a negative U wave in the electrocardiogram as always abnormal. There has been relatively little clinical application of this concept for several reasons. The U wave is frequently difficult to recognize, its onset and termination are often poorly delineated, and determination of its polarity is sometimes impossible even for the experienced observer. Since the origin of the normal U wave is not clearly understood, it is difficult to attribute the finding of an abnormal U wave to any specific physiologic or pathologic event. It seemed that this problem might be approached by studying the polarity and amplitude of the U wave in relation to other components of the electrocardiogram about which there is more theoretical and practical knowledge.

Methods and Materials

The material consisted of electrocardiograms selected at random from the files of the Division of Cardiology of the Philadelphia General Hospital. In some cases (groups A, B, C, and D), 24 additional unipolar chest and abdominal leads were recorded. These included leads made at levels 1 (V′), 2 (V″), and 3 (V‴) intercostal spaces higher than the conventional V-lead level, as well as leads recorded at the level of the ensiform process (VE), and the epigastric level midway between the latter and the umbilicus (V_{ep}). Esophageal leads were obtained in several of these cases. In the remainder of the cases only the 12 standard leads were analyzed (group E).

Results

Group A

This group consisted of electrocardiograms of 22 patients in which the U wave was positive in all the standard precordial leads and exceeded 0.1 mv. in at least 1 lead. There were no cases of myocardial infarction, pericarditis, bundle-branch block, or electrolyte imbalance. None of the patients was receiving digitalis or quinidine therapy.

Relation of U to QRS. There was no consistent relationship between the QRS and the U-wave amplitude in any of the cases studied. In 18 cases the tallest QRS and the tallest U wave were found in different leads. In 4 cases the tallest QRS and the tallest U wave were found in the same lead; in the remaining leads the U-wave amplitude did not bear a constant relationship to the QRS amplitude.

Lead with Tallest U Wave. The tallest U wave was distributed as follows: lead V_{2E}, 5 cases; V_{3E}, 3 cases; $V_{3'}$, 3 cases; V_2, 3 cases; $V_{2'}$, 2 cases; $V_{4'}$, 2 cases; V_3, 2 cases; V_4, 1 case; and V_{4E}, 1 case.

Relation of U Wave to T Wave. In 20 cases the tallest U wave and the tallest T wave were in the same lead. In all leads of these 20 cases, the ratio of the amplitude of the T wave and the U wave remained constant (usually 3:1 to 4:1). In the 2 remaining cases the tallest T wave and the tallest U wave occurred in different leads and the ratio of the T wave and the U-wave amplitudes was not constant.

Group B

This group consisted of the electrocardiograms of 19 cases in which the U wave was negative and deeper than 0.1 mv. in at least 1 precordial lead. There were no cases of myocardial infarction or the other conditions mentioned under group A.

Distribution of Negative U Waves. The U wave was negative in leads V_5 and V_6 in all 19 cases; in $V_{5'}$ in 9 cases; in $V_{6'}$ and V_7 in 8 cases; in V_4 and V_{5E} in 6 cases; in V_{4E} and V_{6E} in 4

From the Division of Cardiology of the Philadelphia General Hospital, Philadelphia, Pa.

This work was aided by grants from the Foundation for Cardiovascular Research, the Eli Lilly Company, Indianapolis, Indiana, and the U. S. Public Health Service Grant H-141 (C7).

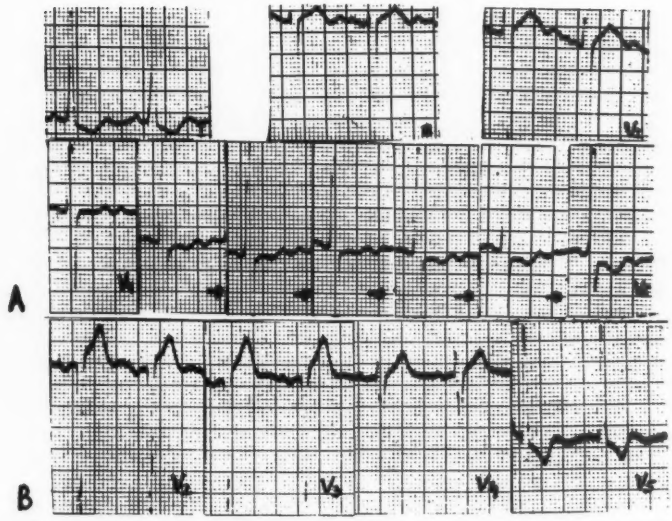

FIG. 1. *A*. Diphasic U waves appearing as a transition between a positive U wave in lead V_4 and a negative U wave in lead V_5, as the electrode was moved from right to left between these leads. The T wave undergoes almost identical changes. *B*. The U wave is positive in leads in V_2 and V_3 and negative in lead V_5. The transition occurs in lead V_4, where the U wave is isoelectric.

cases; in V_{3E}, V_{4ep}, $V_{4'}$ and V_8 in 2 cases; and in V_3, $V_{3'}$, V_{3ep}, and $V_{4''}$ in 1 case.

Lead with Deepest U Wave. The deepest negative U wave was found in lead V_5 in 11 cases, in V_6 in 6 cases, in $V_{5'}$ in 1 case, and in V_4 in 1 case.

Relation of U Wave to T Wave. In 14 cases the polarity of the T wave and the polarity of the U wave were the same and the ratio of the T and U amplitude was constant. The transition between the positive and negative T wave and U wave also occurred in the same precordial leads (fig. 1). The electrocardiograms of all of these cases presented an electrocardiographic "left ventricular strain" pattern. In the remaining 5 cases a negative U wave was found in certain leads with a positive T wave.

Group C

This group consisted of electrocardiograms of 18 patients in which the QRS complexes were wider than 0.12 sec. Three patients showed left bundle-branch block, 3 right bundle-branch block, 10 ventricular premature beats, and 2 a slow idioventricular rhythm.

Relation of U Wave to T Wave. The same polarity of the U wave and the T wave and the constant ratio of the U wave and T wave amplitude were found in 16 cases (fig. 2). In 2 cases with premature ventricular beats in which the T wave was negative, the U wave was positive in certain leads.

The polarity of the U wave could be determined with certainty only in cases in which the duration of the QRS complex did not exceed 0.15 to 0.17 sec. In cases with wider QRS complexes the end of the T wave usually falls either at the apex or beyond the apex of the U wave, causing extensive merging of the T wave with the U wave. If the apex of the U wave is not clearly visible, the determination of the polarity of the U wave is not possible.

Group D

This group consisted of electrocardiograms of 19 patients with T-wave changes due to myocardial infarction or digitalis. In 12 of the 13 cases the pointed, inverted T wave was followed by a positive U wave. In 1 case the U wave was negative in the left precordial leads where the coved, inverted T wave of the infarction was also present. The follow-up

studies of the cases with infarction failed to reveal any changes in the shape or polarity of the U wave during a period of 2 to 8 weeks, although the usual evolution of the T wave took place.

In 6 cases where observations were made during digitalis therapy and in which the U wave exceeded 0.2 mv. in at least 1 lead, no changes in the polarity of the U wave were noted during the period of observation (fig. 3).

Group E

This group included the electrocardiograms of 376 hypertensive patients in whom the systolic blood pressure was above 170 mm. Hg or the diastolic pressure above 100 mm. Hg. The T and U waves were examined only in the precordial leads V_1 through V_6. This analysis was performed only in the cases where the U wave was clearly visible. In all doubtful cases, the following method of identification was applied. The longest Q-T interval in a lead with a monophasic T wave and the longest P-R interval in any of the leads were determined. Both of these intervals were plotted on a tracing of the lead in which the presence of a U wave was suspected. If the interval between the end of the T wave and the beginning of the P wave was less than 0.08 sec., the U wave polarity could not be definitely determined and the tracing was discarded (fig. 4). It became necessary, therefore, to reject almost all tracings

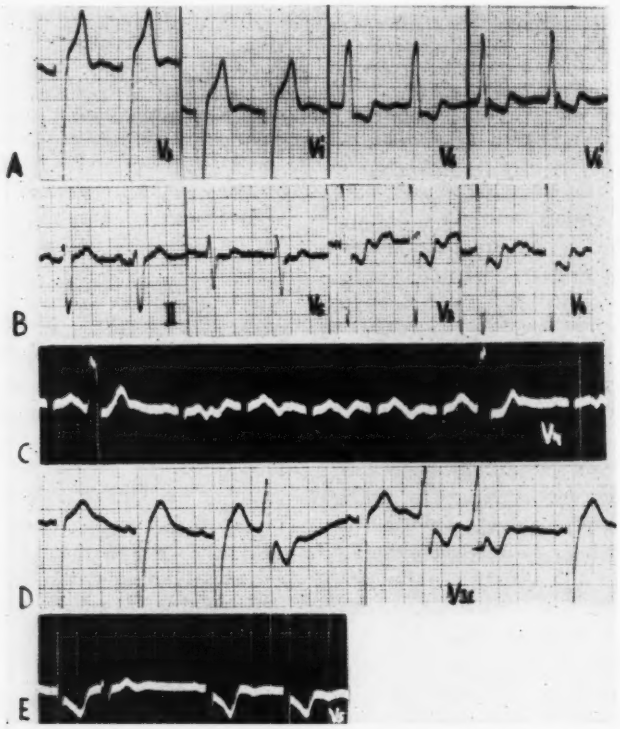

FIG. 2. *A*. In left bundle-branch block, the U wave is positive in leads with a positive T wave and negative in leads with a negative T wave. *B*. In right bundle-branch block, the U wave is negative in leads V_3 and V_4 in which the T wave is also negative. *C*. In the normally conducted beats, a negative U wave follows a small, notched T wave. In the ventricular premature beat, both the U wave and the T wave are positive. *D*. In the normally conducted beats, both the U wave and the T wave are positive. In the ventricular premature beats, both the U wave and the T wave are negative. *E*. In the normally conducted beats, both the U wave and the T wave are negative. In the premature beat, both the U wave and the T wave are positive.

with a heart rate faster than 96 beats/min. In addition, several tracings with a slower heart rate were discarded for 1 of the following reasons: prolongation of the P-R interval, atrial flutter and supraventricular tachycardia with A-V heart block, coarse atrial fibrillation, bigeminal rhythm, conduction disturbances with a QRS duration exceeding 0.17 sec., marked Q-T interval prolongation, and technical errors. A total of 79 tracings was discarded. In the remaining tracings the tallest U wave was found most frequently in the lead with the tallest T wave. The distribution of the tallest positive U waves was as follows:

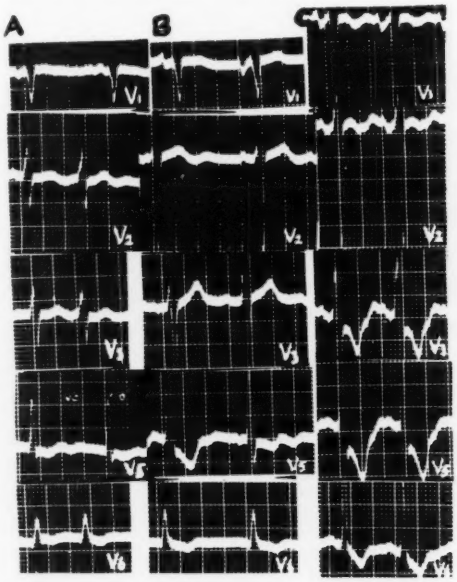

FIG. 3. Electrocardiogram of a 78-year-old white woman (*A*) before digitalis administration and (*B* and *C*) after digitalization. There is progressive inversion of the T wave in leads V_3 through V_6. The polarity of the U wave is unchanged.

Lead	*Cases*	*%*
V_3	115	46
V_4	63	25
V_2	62	25
V_1	6	2
V_5	5	2
	251	100

The relation of the polarity of the T wave and the U wave is presented in figure 5. The cases were subdivided into 6 groups. The largest group includes normal and abnormal tracings with a positive T wave and a positive U wave in all the precordial leads. The second, third, and fourth groups include almost exclusively electrocardiographic patterns of "left ventricular strain" or left bundle-branch block and the difference between those groups are due solely to a different polarity of the U wave. The fifth

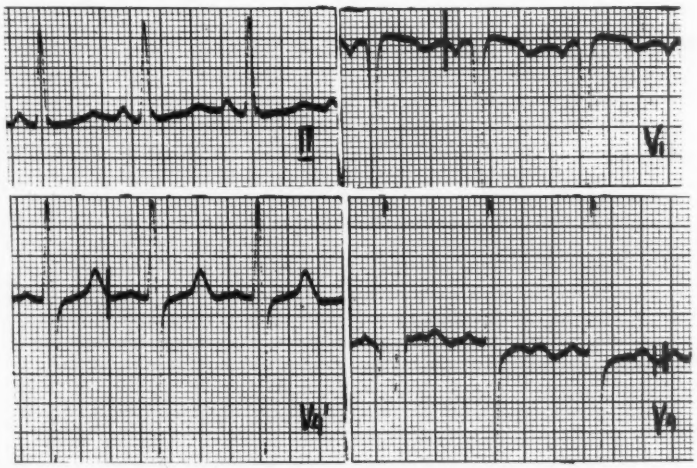

FIG. 4. The U wave appears to be negative in lead V_4. But when the P-R interval, measured in lead V_1, and the Q-T interval, measured in lead V_4, are plotted on the tracing, the T-P interval, measures only 0.08 sec. The determination of the shape and polarity of the U wave in this case is not possible.

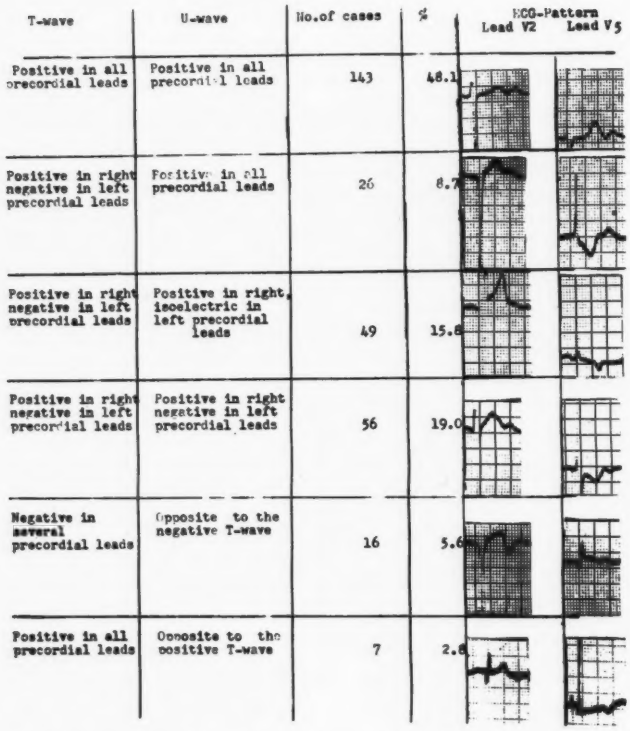

FIG. 5. Relation between the polarity of the U wave and the T wave in 297 cases of hypertension.

group includes cases with a discordance of polarity of the T wave and the U wave in certain leads. There were 5 cases of myocardial infarction with pointed, inverted T waves followed by positive U waves; 7 cases with inverted T waves in leads V_1 and V_2 (juvenile pattern), followed by positive U waves; 1 case with an isolated inversion of the T wave in lead V_4 (transitional T wave), followed by a positive U wave; 1 case of right ventricular hypertrophy pattern with an inverted T wave in leads V_1 and V_2 followed by a positive U wave; and finally 2 cases of "left ventricular strain" pattern in which both the T wave and the U wave were negative in leads V_5 and V_6, but in lead V_4 the T wave was negative and the U wave was positive. It was considered that, with the exception of the last 3 cases, the T-wave inversion in this group was of primary origin. The sixth group included 7 cases with an inverted U wave in several precordial leads in which the T wave was positive. Six of these cases had several other abnormal electrocardiographic features besides the inverted U wave.

This study showed that less than one half of the cases in which the inversion of the T wave is presumably of secondary origin had an inverted U wave in leads with the inverted T wave. Inversion of the U wave without inversion of the T wave was a relatively rare finding in our group. The impression concerning a discordance between T wave and U-wave polarity in the presence of primary T-wave changes was confirmed.

Other Observations

Esophageal leads were taken in several cases in which the U wave exceeded 0.2 mv. and was well separated from the T wave. The U wave was usually obscured by artifacts and could be identified with certainty in only 3 cases. The polarity of the U wave was the same as the

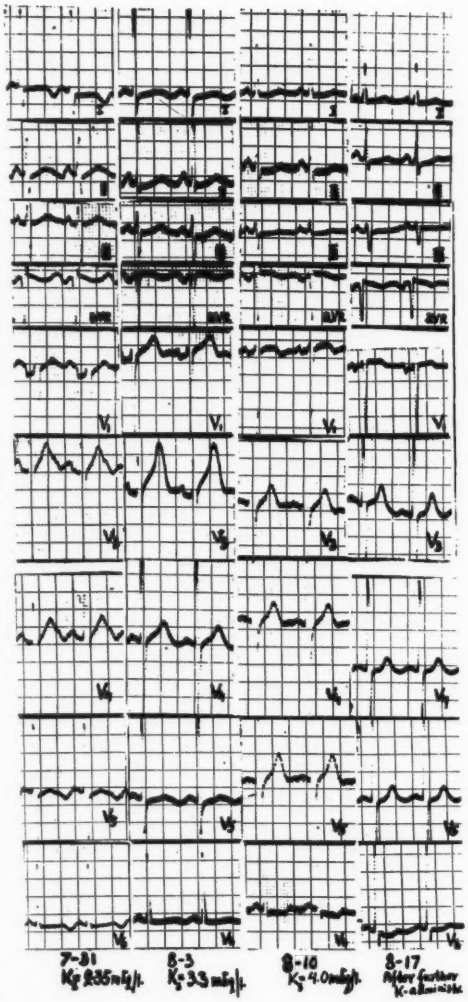

FIG. 6. A deep negative U wave in leads I and V_3 through V_6 in hypopotassemia decreases in amplitude after potassium administration. The polarity remains unchanged.

polarity of the T wave and the ratio of the T wave and the U wave amplitude was the same as in the precordial leads.

The increase of the U-wave amplitude in hypopotassemia has been observed in 2 cases in which the U wave was negative. As previously suspected,[1] hypopotassemia does not change the polarity but affects only the amplitude of the U wave (fig. 6).

A change in the polarity of the U wave was

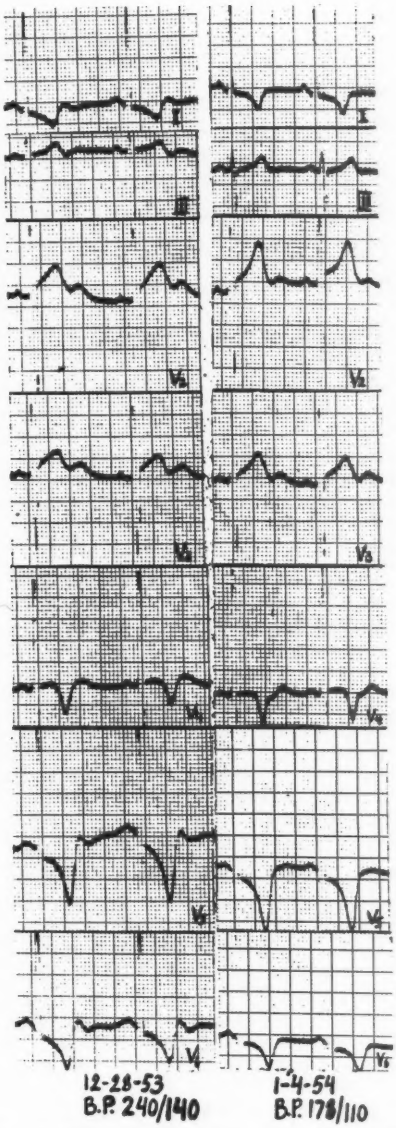

FIG. 7. Electrocardiogram of a 54-year-old Negro man with hypertension. A fall in blood pressure is accompanied by a change from a negative U wave in leads I and V_6 to an isoelectric U wave in these leads. In lead V_5, the change was from a negative U wave to a positive U wave.

observed in several cases following a change of heart rate. In some cases the faster heart rate was accompanied by a negative, and a slower rate by a positive U wave. In certain cases the

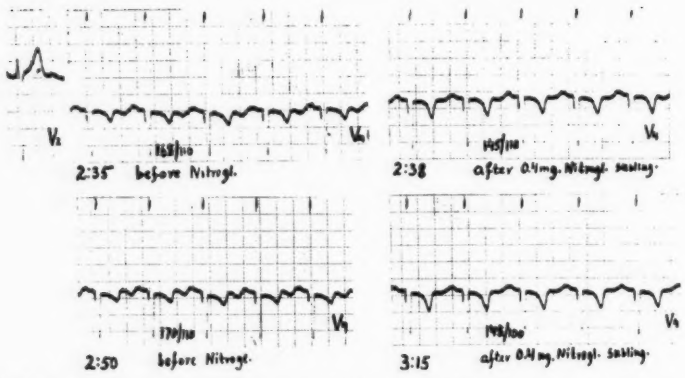

FIG. 8. A change from a negative U wave to an isoelectric U wave after nitroglycerin administration in the same patient on 2 occasions. Note accompanying T-wave changes.

heart rate was unchanged or even faster in the presence of positive U waves. In 3 cases of the latter type, the blood pressure was found to be higher in the presence of a negative U wave (fig. 7). In 1 case, repeated administration of nitroglycerin was associated with a change from an inverted to an isoelectric U wave accompanied by a drop in the blood pressure (fig. 8). In all of the described cases U wave changes were accompanied by at least some T-wave changes, and therefore it was impossible to decide whether or not the changes of the U-wave polarity were primary.

DISCUSSION

Variations in the interpretation of the U wave are due largely to difficulties in its identification. It has been stated that the U wave may be confused with an apparent terminal "dipping" of the T wave[2] and with a depression of the T-U junction.[3] Part of the P wave may also be mistaken for the U wave, making accurate determination of the P-R interval imperative.[4] It has also been found that the U wave cannot be clearly delineated when the heart rate is more than 110/min.[4, 5] In our experience, clear demarcation of the U wave requires plotting both the Q-T and the P-R intervals. The application of this method leads us to the conclusion that in the majority of cases, the determination of the shape and polarity of the U wave is impossible when the heart rate is above 96/min. The similarity in the shape of the U wave and the T wave as well as the frequent occurrence of tall U waves in tracings with tall T waves has been noted previously.[4-9] This similarity probably accounts for the fact that the U wave was once called "a dicrotic T wave."[10]

It has been reported that digitalis may influence the polarity of the U wave.[11] This has not been observed in our experience.

We have found that in electrocardiograms of hypertensive patients, the majority of negative U waves accompany secondary T-wave inversion. But since in only about one half of the cases with presumably secondary T-wave inversion was there an accompanying U-wave inversion, it seemed to us that the inversion of the U wave might be a later event. Some of our observations of the evolution of the "left ventricular strain" pattern led us to believe that there is a gradual transition from a positive U wave to an isoelectric U wave to a negative U wave in the left precordial leads. A negative U wave in the presence of a positive T wave was rarely found. Such a finding may be due to either a primary inversion of the U wave or to a change in the polarity of the T wave from negative to positive in a case with a previously inverted U wave. The latter was observed during the development of a peaked, positive T wave after subendocardial infarction or acute coronary insufficiency. In some of the observed cases of left ventricular hypertrophy pattern, the U wave was negative in the left precordial leads while the T wave was still positive. All such cases were associated with

narked hypertension and in 2 cases this finding vas present during exceptionally fulminating nalignant hypertension. Negative U waves in he presence of positive T waves were almost lways associated with other electrocardio- graphic abnormalities, particularly with low T vaves. We have seen only 1 case in which a negative U wave accompanied a normal T vave. Only a few cases of this kind have been published[8, 12, 13] and in 1 of them (fig. 1 of Twiss and Sokolow's article[14]) the T wave became deeply inverted after exercise.

In all the observed cases in which a negative U wave became positive after slowing of the heart rate or a drop in blood pressure there were some concomitant T-wave changes. This was also observed in cases in which a negative U wave became positive after sympathectomy (figs. 8 and 12 of the article by White and co-workers[15]).

Summary

The ratio of the amplitude of the QRS complex to the amplitude of the U wave varies in different leads of the same electrocardiogram. In the majority of electrocardiograms, the U wave has the same polarity as the T wave and the ratio of the U wave and T wave amplitude is relatively constant in all leads. The tallest positive U wave is usually observed in the area of leads V_2 to V_4. The deepest negative U wave is usually observed in the area of leads V_5 to V_6. Secondary changes of the T wave are very frequently accompanied by similar changes of the U wave. T-wave changes caused by myocardial infarction and digitalis are usually not accompanied by changes of the polarity of the U wave.

The electrocardiograms of 297 cases of hypertension were divided into 6 groups on the basis of the relationship between the polarity of the T wave and the U wave. Both waves were positive in all precordial leads in 48.1 per cent of the cases. Negative U waves were found in 21.8 per cent of the cases and these were predominantly in the leads with negative T waves. A negative T wave in the left precordial leads was accompanied most frequently by a negative, less frequently by an isoelectric, and least frequently by a positive, U wave. An inverted U wave in the presence of an upright T wave was found in only 2.8 per cent of the cases. A change from a negative to a positive or isoelectric U wave was observed after slowing of the heart rate, a drop in blood pressure, and nitroglycerin administration.

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XIII. Prognostic Significance of Negative U Waves in the Electrocardiogram in Hypertension

By Robert L. Kemp, M.D., Borys Surawicz, M.D., John C. Bettinger, M.D., Harry Gottlieb, M.D., and Samuel Bellet, M.D.

NEGATIVE U waves are usually preceded by negative T waves. It also seems that only secondarily inverted T waves are followed by inverted U waves. It was found by us, however, that the U wave was inverted in less than one half of the electrocardiograms that showed presumably secondary inversion of the T wave. The presence of an upright U wave in leads where the T wave was already inverted could be explained by the existence of a time lag between the inversion of the T wave and the inversion of the U wave in the evolution of a "left ventricular strain pattern." An isolectric U wave would probably signify a transitional phase preceding actual U wave inversion. Our previous clinical observations tended to support such a concept. If this assumption was correct and the occurrence of an inverted U wave was a late finding in "left ventricular strain patterns," then an inverted U wave should be associated with clinical findings of more advanced disease of the left ventricle.

Methods and Materials

Because the majority of negative U waves are found in electrocardiograms of patients with hypertension, a group of 287 patients with elevated blood pressures who had electrocardiograms in which the U-wave amplitude and polarity could be accurately determined were selected from the files of the Division of Cardiology of the Philadelphia General Hospital. The method of selection was described in the previous communication.[1] The interpretations of the electrocardiograms were performed without knowledge of the clinical findings. The latter were obtained later from the hospital records.

The electrocardiographic diagnosis (table 1) of "left ventricular hypertrophy" was based on the presence of left axis deviation with the sum of the deepest S wave in the right precordial leads plus the tallest R wave in the left precordial leads exceeding 35 mm. without T-wave inversion. "Left ventricular strain" was defined as the left ventricular hypertrophy pattern plus T-wave inversion in the left precordial leads.

In analyzing the clinical findings, the degree of congestive heart failure was determined on the basis of the physical examination performed at the time the electrocardiogram was taken. Renal function was determined by urinalyses and blood urea nitrogen values, (available in all cases), phenolsulfonphthalein tests, Fishberg concentration tests, intravenous pyelography, blood creatinine levels, and urea clearance tests (obtained in many cases). Heart size was determined by teleroentgenogram or orthodiagram. The fundoscopic examinations were performed by a staff ophthalmologist.

In evaluating the mortality (table 2), all deaths occurring within 6 months of the time the electrocardiogram was taken were recorded and the cause of death noted.

Results

The sex, color, and age distribution of the cases studied are presented in table 3. The distribution by sex and color was about the same for both the negative and positive U-wave groups. The age range and distribution were also similar. It should be noted, however, that the Negro women, who made up the largest single group, were appreciably younger than their white counterparts in both the negative and positive U groups. The Negro men were also younger than their white counterparts.

Blood pressure determinations in the cases studied are presented in table 4. The average diastolic pressure and the average mean pressure were significantly higher in the negative U-wave group whereas the pulse pressure was nearly equal in both groups.

The clinical findings in the negative and positive U groups are presented in table 5

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TABLE 1.—*Electrocardiographic Diagnosis*

Pattern	Positive U		Negative U	
	Number	Per cent	Number	Per cent
Normal	62	28.0	1	1.5
Nonspecific T-wave changes	30	13.6	3	4.5
Left ventricular hypertrophy	45	20.4	8	12.1
Left ventricular "strain" pattern	65	29.4	49	74.2
Left bundle-branch block	4	1.8	0	0
Right bundle-branch block	7	3.2	2	3.0
Infarction	6	2.7	3	4.5
Other*	2	.9	0	0
Total	221	100	66	100

* One case of right ventricular hypertrophy and 1 case of pericarditis.

TABLE 2.—*Mortality within Six Months*

Cause of Death	Positive U		Negative U	
	Number	Per cent	Number	Per cent
Myocardial infarction	1	.5	3	4.6
Uremia	2	.9	9	13.6
Cerebrovascular accident	2	.9	4	6.0
Congestive heart failure	5	2.3	3	4.6
Unrelated to hypertensive cardiovascular disease	3	1.4	3	4.6
Total	13	5.9	22	33.4

TABLE 3.—*Sex, Color and Age Distribution of Two Hundred Eighty-two Cases*

Patients	Positive U			Negative U		
	Number	Per cent	Av. Age	Number	Per cent	Av. Age
White men	36	16.7	62	9	13.6	68
Negro men	54	25.0	57	16	24.2	58
White women	36	16.7	62	12	18.2	67
Negro women	90	41.7	55	29	44.0	56
Total	216	100.0	18–88	66	100.0	16–87

TABLE 4.— *Blood Pressure in Two Hundred Twenty-one Positive U Cases and Sixty-Six Negative U Cases*

Blood Pressure	Positive U (mm. Hg)	Negative U (mm. Hg)
Average systolic	194	214
Range of systolic	144–260	140–280
Average diastolic	109	130
Range of diastolic	70–190	55–180
Average pulse	85	84
Average mean	137	158

TABLE 5.—*Clinical Findings in Two Hundred Twenty-one Positive U Cases and Sixty-six Negative U Cases.*

Clinical findings	Positive U		Negative U	
	Number	Per cent	Number	Per cent
Congestive heart failure				
No failure, no treatment	132	60.0	17	25.7
No failure but receiving treatment	35	15.8	7	10.6
In failure, but no treatment	15	6.7	13	19.7
In failure, receiving treatment	39	17.6	29	44.0
Heart size				
Normal	79	35.7	4	6.1
Slight to moderate enlargement	102	46.2	37	56.1
Marked enlargement	22	10.0	15	22.7
No data available	18	8.1	10	15.1
Renal function				
No evidence of impairment	125	56.5	19	28.8
Evidence of some impairment	76	34.4	22	33.3
Uremia	9	4.1	20	30.3
No date	11	5.0	5	7.6
Cerebral complications				
Cerebrovascular accidents and severe encephalopathy	37	16.7	20	30.3
Mild, or no cerebral symptoms	184	83.3	46	69.7
Fundoscopic findings				
Normal	15	16.3	3	8.6
Grades I to III hypertensive angiopathy	69	75.0	27	77.1
Grade IV hypertensive angiopathy	2	2.2	3	8.6
Diabetic retinopathy	6	6.5	2	5.7
No data available	129		31	

ubjects with positive U waves in the electrocardiogram showed a relatively small incidence f heart failure and cardiac enlargement. There as a higher incidence of severe failure despite herapy and of marked cardiomegaly in the negative U cases. There was a much higher incidence of uremia and a much lower incidence of negative renal findings in the negative U group. The negative U-wave cases showed a much higher incidence of cerebrovascular

accidents and severe encephalopathy. The number of fundoscopic examinations performed was too small for statistical analysis. There appeared to be a trend toward more advanced hypertensive retinopathy in the negative U group.

Electrocardiographic diagnoses in the positive and negative U cases are presented in table 1. The most significant differences between the 2 groups were the almost complete absence of normal tracings and the predominance of "left ventricular strain" patterns in the negative U group.

The mortality in the 2 groups is presented in table 2. There was a 33.4 per cent mortality in the negative U group within 6 months of the time the tracing was taken. The positive U group sustained only a 5.9 per cent mortality in the same period. Uremia was the most common cause of death among patients in the negative U-wave group.

From this study it was concluded that patients with hypertension who have negative U waves in the left precordial leads of the electrocardiogram have higher average diastolic and mean blood pressures, a higher incidence of "left ventricular strain" patterns, more advanced congestive heart failure, a higher incidence of marked cardiomegaly and uremia, more serious cerebrovascular complications, and a higher mortality than patients with positive U waves.

Table 1 showed that most cases with nega-

TABLE 6.—*Evaluation of Clinical Data in One Hundred Fourteen Cases with Left Ventricular "Strain" Pattern*

Clinical findings	Positive U 65 Cases		Negative U 49 Cases	
	Number	Per cent	Number	Per cent
Congestive heart failure				
No evidence of failure—no therapy	30	46.2	11	22.5
No evidence of failure—with therapy	15	23.0	7	14.3
Patient in failure—no therapy	8	12.3	8	16.3
Patient in failure—with therapy	12	18.5	23	46.9
Renal function				
No evidence of impairment	30	46.2	11	22.5
Some impairment	26	40.0	23	46.9
Severe uremia	3	4.6	12	24.5
No data	6	9.2	3	6.1
Heart size				
Normal	16	24.6	3	6.1
Slight to moderate enlargement	38	58.5	27	55.1
Marked enlargement	8	12.3	16	32.7
No data	3	4.6	3	6.1
Mortality	7	10.8	13	25.6

TABLE 7.—*Cases of Hypertension with Negative U Waves and Positive T Waves*

Patient ♀	Age	Blood Pressure	Electrocardiogram	Congestive heart failure	Cardiomegaly	Renal Impairment	Retinopathy	Cerebral manifest.	Remarks
V.L.	49	260/160	Left ventricular hypertrophy	No failure—but therapy	Slight	Some	Grade III	—	Sympathectomy
C.F.	87	210/120	Left ventricular hypertrophy	No failure—no therapy	—	None	—	CVA	Death—CVA
I.L.	40	274/156	Left ventricular hypertrophy	Failure—receiving therapy	Moderate	Uremia	Grade IV	None	Death—malignant hypertension
E.J.	55	210/114	Left ventricular hypertrophy	No failure—no therapy	Moderate	None	Grade II	None	Diabetes
D.K.	16	190/130	Nonspecific T-wave changes	No failure—no therapy	Moderate	Uremia	Grade IV	None	Death—Periarteritis nodosa
E.J.	54	170/100	Normal	No failure—no therapy	Normal	—	—	None	Cholecystitis
H.B.	60	260/140	Nonspecific T-wave changes	No failure—no therapy	—	None	—	CVA	Death—CVA

ive U waves were associated with "left ventricular strain" patterns. This pattern in itself epresents advanced left ventricular disease. Therefore, it became necessary to determine whether the clinical results were due to a preponderance of strain patterns in the negative U group or whether the negative U wave per se was the determining factor. For this purpose, all electrocardiograms with a "left ventricular strain" pattern were divided into 2 groups, 1 with negative U waves and the other with positive or isoelectric U waves. These 2 groups, in which the only electrocardiographic difference was limited to the polarity of the U wave, were compared in the previously described manner. The results are presented in table 6.

The group with negative U waves showed a higher incidence of advanced congestive heart failure despite therapy, marked cardiomegaly, severe uremia, and a higher mortality. The group with positive or isoelectric U waves showed a much higher incidence of absence of heart failure, cardiomegaly, and renal impairment. The mortality in the latter group was also lower. There was no appreciable difference in the incidence of cerebrovascular complications (32.7 per cent in the negative U group and 32.3 per cent in the positive U group). There was only a slight difference in the incidence of severe hypertensive angiopathy (hemorrhages, exudates, and papilledema), 14.3 per cent in the negative U group and 9.2 per cent in the positive U group.

Among the 66 cases of hypertension with negative U waves there were 7 cases in which no T-wave inversion was present in any of the precordial leads. The clinical data and electrocardiograms of these cases are presented in table 7. All of the above cases were female and the average age was 51 years, which is slightly younger than the average age of the Negro woman in the entire negative U wave group (table 3). The average systolic blood pressure was 223 mm., the average diastolic blood pressure was 131 mm., and the average mean pressure was 161 mm. Hg. These values are also higher than the average in the negative U-wave group (table 4). There were 4 deaths. Two patients died of uremia: 1 had malignant hypertension and the other periarteritis nodosa. The other 2 patients died of cerebrovascular accidents. This mortality of 57 per cent is also higher than in the entire negative U-wave group (table 2). The patient with periarteritis nodosa was only 16 years of age and constituted the youngest case with negative U waves in the series. Of the remaining 3 cases, 1 had diabetes mellitus and 1 had acute cholecystitis. This last case had a normal electrocardiogram and no other cardiovascular abnormalities.

Summary

Negative U waves were found in 23 per cent of 287 electrocardiograms of hypertensive patients. The group of patients with negative U waves showed higher average diastolic and mean blood pressures, more advanced congestive heart failure, a higher incidence of marked cardiomegaly and uremia, more serious cerebrovascular complications, and a higher mortality than the group with positive U waves.

Normal heart size, normal electrocardiographic patterns, and absence of evidence of renal impairment or congestive heart failure occurred more commonly in the group with positive U waves. Negative U waves were found in 43 per cent of 114 cases of "left ventricular strain" pattern in hypertensive patients.

In the presence of "left ventricular strain" pattern, the patients with negative U waves had more advanced congestive heart failure, a higher incidence of marked cardiomegaly and uremia, and a higher mortality than the patients with positive or isoelectric U waves.

A concept has been advanced that in the evolution of the "left ventricular strain" pattern, the inversion of the U wave is a late event that follows the inversion of the T wave by a certain time lag. In the few cases in which an inverted U wave followed a positive T wave, the morbidity and mortality were very high.

A negative U wave constituted the only abnormal finding in 1 case.

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XIV. Clinical Study of the Abnormalities of the Terminal Complex TU-U of the Electrocardiogram

By Joseph Lambert, M.D.

THE clinical studies of the terminal complex were limited in the past to abnormalities of the U wave. However, Palmer[1] pointed out the possibility of abnormalities of the T-U junction. Diphasic U waves were studied by Papp[2] and the conversion to negative U waves of diphasic U waves was studied by Holzmann.[3]

The terminal complex of the electrocardiogram, which immediately follows the T wave, may be looked upon as being formed in the normal subject by the U wave itself and by an isoelectric segment (T-U) joining the T and U waves. The T-U segment often does not appear because of merging of the T and U waves, but it is obvious in cases with negative U waves (figs. 1, 2, 3). Under the name of "abnormalities of the T-U segment" are grouped, for descriptive purposes, waves of variable shape that may appear between the T wave and the U wave. Occasionally it may be difficult to dissociate a negative T-U segment from the first phase of a diphasic U wave. The measurement of Q-T and Q-aU durations according to Lepeschkin and Surawicz[4] is useful, but we can recognize neither the beginning nor the end of an abnormal T-U segment; this could be masked in part by the T wave (fig. 4) and could, on the other hand alter the shape of a remaining normal U wave.

Among 3,700 electrocardiograms recorded in the 12 routine leads, the tracings of 245 patients exhibited abnormalities of the terminal complex TU-U; the cardiac diseases consisted of hypertension, 131; coronary disease, 45; myocardial infarction, 29; aortic disease (stenosis or regurgitation), 19; other cardiovascular diseases, 18; cardiac neurosis, 3.

Results

I. The TU-U abnormalities were divided as follows: (1) T-U deviation: often negative (56 cases), V-shaped or cup-shaped (negative T-U segment) (fig. 2); sometimes positive (positive T-U segment), followed by a negative U wave (figs. 3 and 4). Both the T and U waves often seemed to participate in the formation of the T-U segment. (2) diphasic or negative U waves. (3) association of (1) and (2) in the same electrocardiogram.

II. An electrocardiographic pattern was

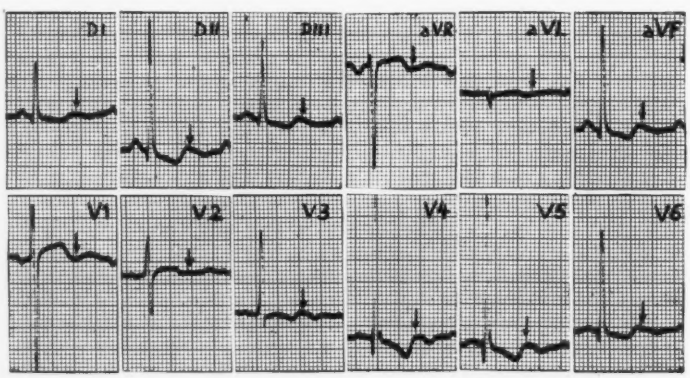

Fig. 1. A 72-year-old woman. Hypertension, coronary disease. Left ventricular strain pattern. Isoelectric T-U segment. Negative U wave in leads II, aV_F, V_2, V_4, V_5, and V_6. Arrows mark the end of T as determined in V_1 and V_6.

described consisting of association of a positive symmetrical T wave (with depressed or plateau-shaped S-T segment) and TU-U abnormalities (T-U deviation, diphasic or negative U wave), which appeared usually in lead I, occasionally in aV_L but was most obvious in the left precordial leads; the descending branch of the T wave was always notched by the T-U segment, whatever its level or its shape (fig. 4). In certain cases

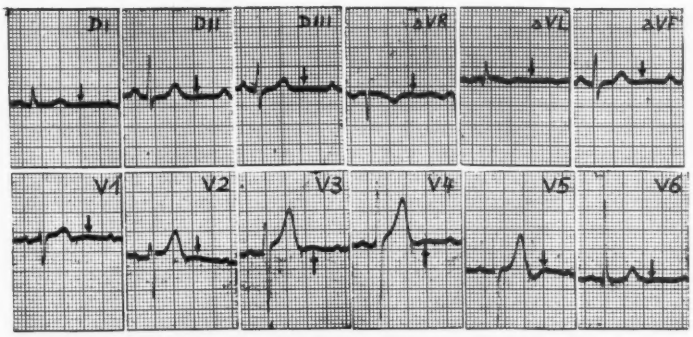

FIG. 2. A 69-year-old man. Hypertension. Negative T-U segment in V_4 and V_5, appearing as a negative extension of the T wave. It is in contrast with the generally weak amplitude of the U wave. One year later the U wave became negative.

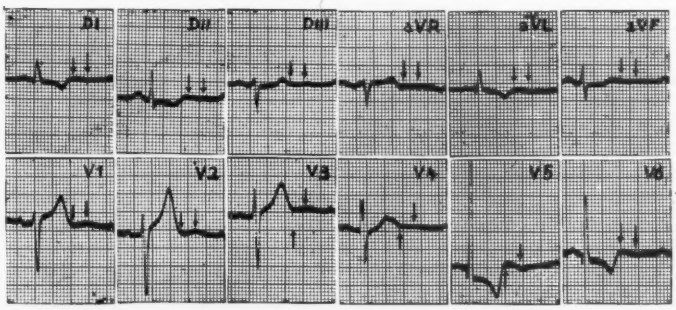

FIG. 3. A 69-year-old man. Hypertension, left ventricular failure. Left ventricular strain pattern. In V_5 and V_6, elevated T-U segment, negative U wave. Arrows mark the end of T and the apex of U as determined in V_1.

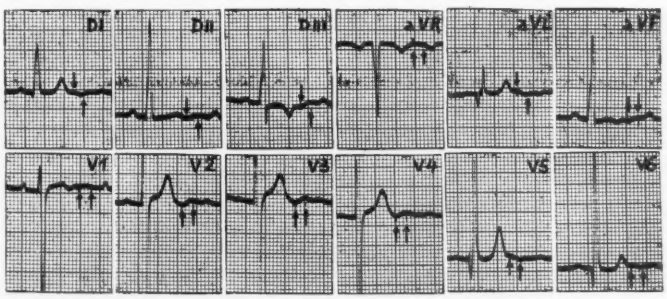

FIG. 4. A 21-year-old woman. Aortic regurgitation with big left ventricle. Positive symmetrical T wave with negative U wave in leads I, aV_L, V_5, and V_6. T-U segment elevated in aV_L and V_5. Arrows mark the end of T and the apex of U as determined in V_4.

such a pattern occurred only after an exercise test. It was met in 54 cases where left ventricular strain was strongly suspected, (in 49 cases as the sole abnormal pattern, in 5 cases associated with a rudimentary left ventricular strain pattern).

III. In 121 of the 245 cases, abnormalities of the TU-U complex were superimposed on an important electrocardiographic pattern. The left ventricular strain pattern (75 cases left, 1 case right) was associated with a negative U alone in 31 (fig. 1), negative U with elevated T-U in the same lead in 12 (fig. 3), negative U with depressed T-U in a different lead in 18, diphasic U in 2, depressed T-U in 11, and elevated T-U in 2 cases. These abnormalities usually appeared in the same leads as the abnormalities of S-T and T. The bundle-branch block pattern (15 cases left, 1 case right) was associated with negative U in 16 cases and was accompanied by depressed T-U in 3 cases in leads showing negative T waves. In myocardial infarction (29 cases), leads showing the coronary T wave pattern had negative U waves in 21 cases, diphasic U waves in 1 case, and depressed T-U in 3 cases; leads not showing the coronary T wave pattern had depressed T-U in 4 cases, of which 1 also showed negative U waves.

Conclusions

One has to be aware of the polymorphism of the abnormalities of the terminal-complex TU-U and of the occurrence of deviations with deformations of the intermediate section between T and U (T-U segment).

Abnormalities of T-U and U are met in very different cardiac diseases, but most frequently in hypertension, aortic and coronary disease; they are isolated in a part of the cases.

U-wave negativity more often accompanies the signs of severe myocardial damage than do the other abnormalities of the TU-U complex.

Positive symmetrical T waves with TU-U abnormalities may be considered as a minor sign of left ventricular strain.

The abnormalities of the T-U segment could be caused by afterpotentials while the abnormalities of the U wave could result from local inequalities in the stretching of the ventricular muscle during the diastolic phase of rapid filling. However, as the 2 kinds of abnormalities may coexist in the same electrocardiogram, the problem of interpretation remains a complicated one.

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XV. U Wave in Coronary Disease

By Cornelio Papp, M.D.

ANY investigation dealing with the U wave has to surmount many difficulties: the wave is small and appears often only as a slight undulation of the 0 line; it varies in size and shape with respiration, it fuses with the following P at a heart rate over 100 and with the preceding T at a rate of 40 to 50.[1] The T-U fusion seems to be rather related to the Q-T duration than to the rate itself.

Only 70 to 80 per cent of the records can thus be selected for study; the rate should be 60 to 80, the base line steady, and U should be of a measurable height. Anterior chest leads (V_2, V_3, and V_4) are more suitable for this purpose except in vertical hearts where the largest deflection may appear in leads II or III and aV_F.

In this study, based on approximately 300 cases of coronary disease, the attention was focused on the abnormal U wave, which consisted of 6 types. (1) The inverted U wave has been recognized as abnormal ever since it was first reported by Nahum and Hoff[2, 3] in 1939.

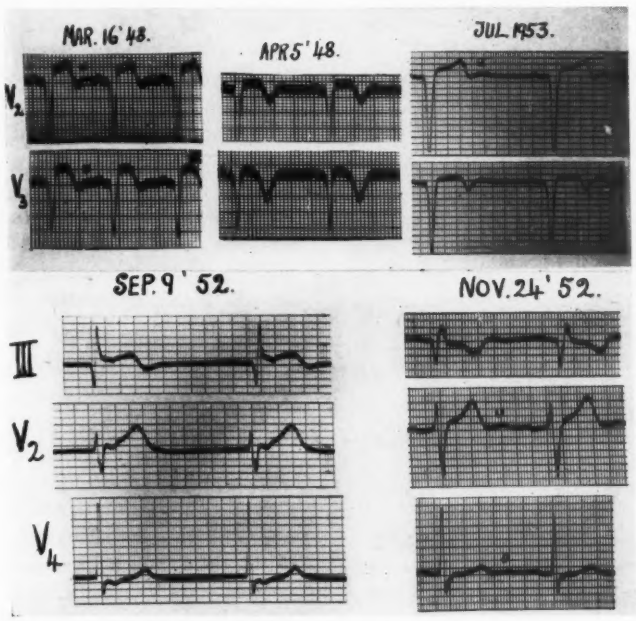


Fig. 1. (*Top*) U wave in patient with anteroseptal infarction. It is present during the acute stage, disappears during deep T negativity, reappears after healing.

Fig. 2. (*Bottom*) Absence of U during septal involvement of posterior infarction (nodal rhythm with retrograde P); its reappearance when septal involvement subsides.

There are, however, other U changes that are exceptional in normal records such as (2) diphasic U waves in left precordial leads, and (3) U of a delayed appearance (eT-aU greater than 0.12 sec.).[4]

Minor abnormalities include (4) T:U ratio less than 1:1 or 1:2. Under normal conditions T in V_2 or V_3 is 5 to 20 times taller than its

From the Cardiac Department, London Chest Hospital, London, England.

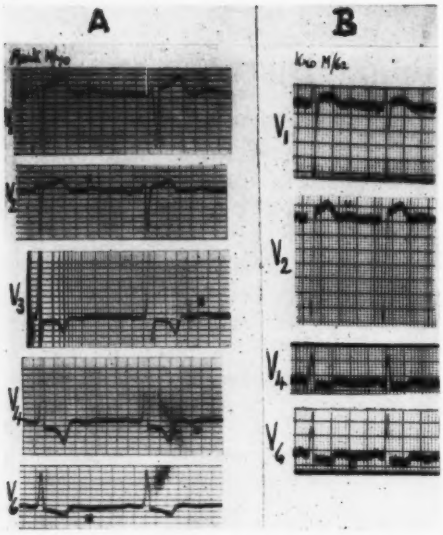


FIG. 3. U wave in patient with angina. *A*. U delayed in V_2, inverted in V_4, V_5, and V_6. *B*. U concordant with R-T and not with T.

FIG. 4. U inverted in lead III and aV_F in patients with angina and vertical heart.

fellow U. A U wave as tall as T or half the size of T is exceptional in normal records. (5) Discordant upright U waves. U is conditioned not only in height but in direction to T and this applies as much to normal as to abnormal records. An upright U that follows an inverted T in V_3 through V_6 is abnormal. (6) Absent U waves. Though U is often not of a measurable height in normal records, it is exceptional that the 0 line should not show a slight undulation at least in 2 of the 12 leads commonly recorded.

U IN ACUTE CARDIAC INFARCTION

During the acute stage of anterior infarction (high S-T take-off) U is upright; when terminal T inversion develops U disappears because it is buried in the prolonged Q-T period; when the Q-T period shortens U may reappear again and then follows the direction of T. At the healing stage, when T becomes upright, U also returns to normal (fig. 1).

Posterior infarction does not influence the U wave of the anterior chest leads except when through septal invasion ectopic bradycardia develops, when U is obliterated by the prolonged Q-T period. Here U reappears when the septal invasion subsides and the rate becomes normal (fig. 2).

Admittedly this is a schematic version that has many exceptions; however, the U-wave changes in acute infarction are of secondary importance as other abnormal features are present. It is in chronic coronary disease, where the S-T changes are of a lesser degree, that the presence of abnormal U waves may help in the diagnosis.

U WAVE IN ANGINA AND CORONARY INSUFFICIENCY

In angina pectoris inverted U waves never appear in V_2 or V_3; at the most U is isoelectric in these leads. Inversion is seen in V_4, V_5, and V_6 and it develops gradually from V_2 onwards. The T-aU distance lengthens in V_2, U becomes diphasic in V_3 and V_4 and inverted in V_4, V_5, and V_6 (fig. 3*A*). U inversion at times is conditioned by S-T depression and not by T inversion (fig. 3*B*). An inverted U wave may be the only sign of coronary disease. It may be more prominent in lead III and aV_F when the heart is vertical (fig. 4).

During the effort test in coronary disease an upright U or an isoelectric U may become inverted while the S-T interval remains isoelectric (fig. 5*B*); a negative effort test increases the voltage of U (fig. 5*A*). It is however, exceptional that this should be the only abnormality in the electrocardiogram. Under effort an abnormally inverted T may become upright (paradoxical reversal); at the same time U returns to normal through a diphasic pattern

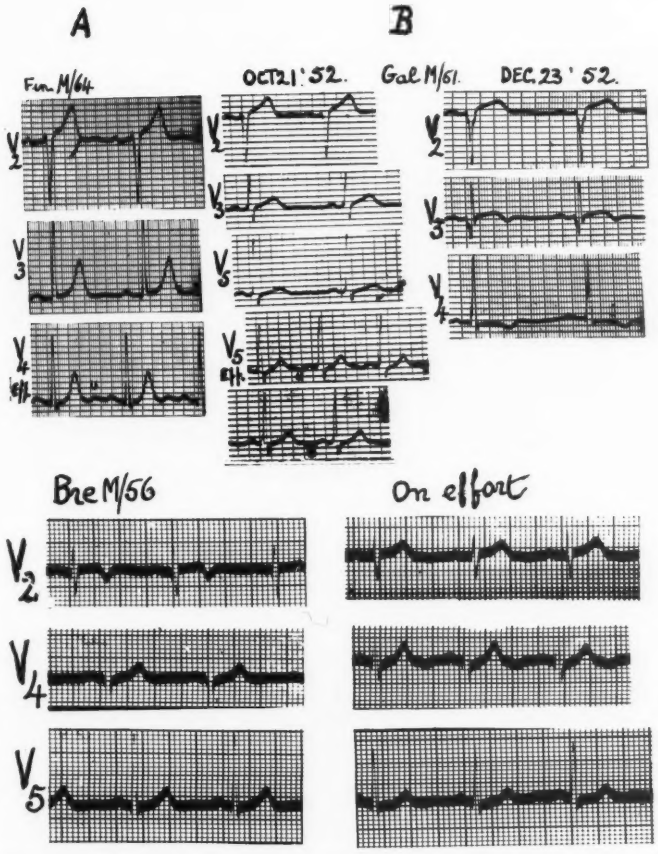


FIG. 5. (*Top*) *A*. U increases after negative effort test. *B*. U inversion after positive effort test; anterior infarction 2 months later.

FIG. 6. (*Bottom*) U inversion on effort associated with paradoxical reversal of T in V_2.

(fig. 6). More often a pathologic S-T depression is associated with the inversion of U (fig. 7).

U wave inversion is not necessarily abnormal; it is seen in advanced age without heart disease though it is difficult to be certain whether the coronary circulation is normal at this age even if there is no angina (fig. 8).

In many patients with U inversion after effort, there is no U wave to be seen in the resting record; in fact the complete absence of U waves, exceptional in normal records, was found in 6 per cent of patients with angina (fig. 9*A*, *B*). In figure 9*C*, U waves failed to appear after effort.

An abnormal T:U ratio may depend on a diminished voltage of T, on an increased voltage of U, or on both. In figure 10*A* and *B*, left ventricular strain was present as well, which diminished T and may have increased U in right ventricular leads; in figure 10*C* the disproportion was due to the small voltage of T only. All 3 had moderately severe angina. Digitalis also realizes identical conditions by the R-T changes it produces and by the absolute increase in the voltage of U (fig. 11). However, this feature may not be necessarily abnormal. Occasionally neurocirculatory asthenia may show taller U than T waves in leads II and III (fig. 12).

In presence of an abnormal T:U ratio the U wave may be confused with the second peak of a bifid T wave. This can be easily avoided by

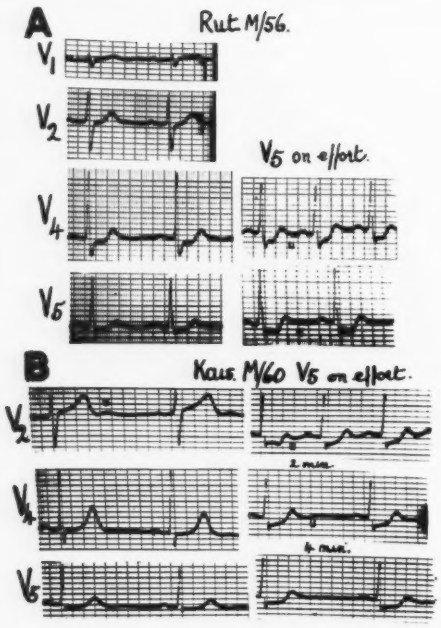
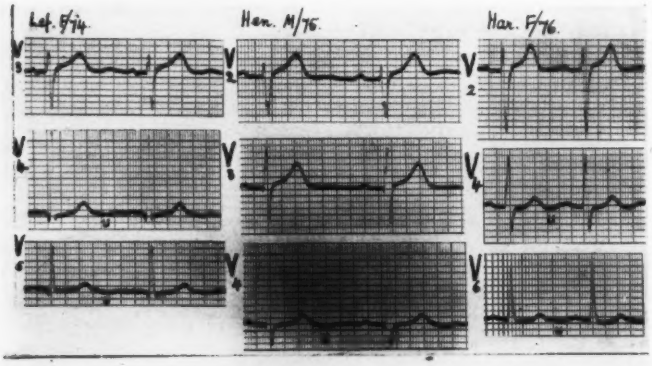


FIG. 7. U inversion on effort associated with R-T depression. *A*. Absent U waves in resting record; *B*. Regression of U inversion through its diphasic pattern.



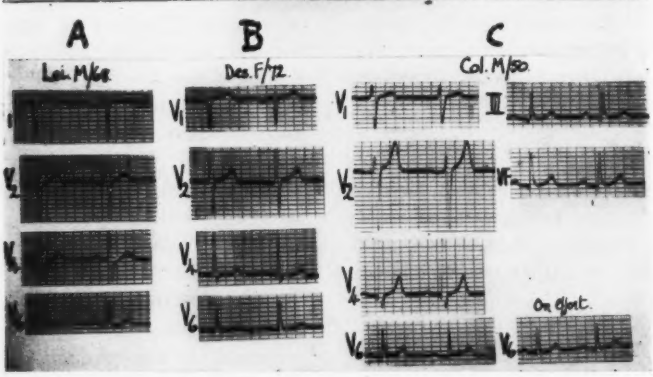


FIG. 8. (*Top*) U inversion in old age. Heart normal, no angina.
FIG. 9. (*Bottom*) *A* and *B*. Absent U waves in patients with severe angina. *C*. No U wave on effort.

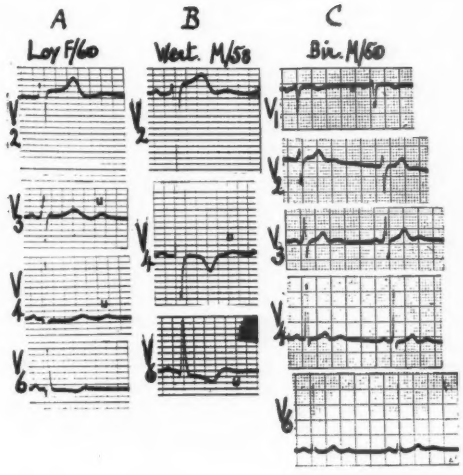


FIG. 10. Abnormal T:U ratio and discordant U in V_4 due to increase of U in left ventricular hypertrophy in *A* and *B*, and to decrease of T in *C*. All 3 with angina.

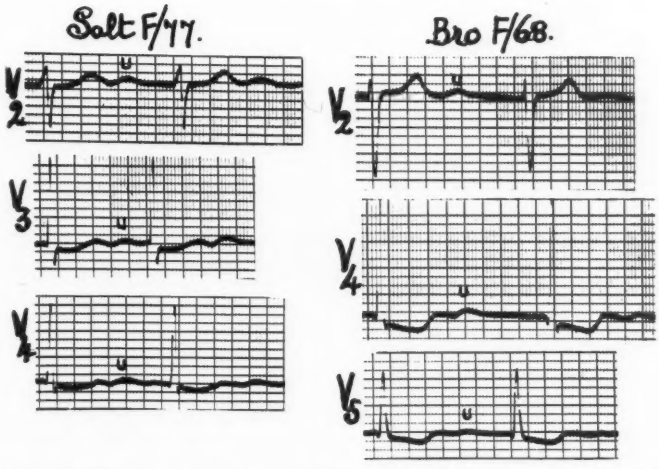


FIG. 11. Abnormal T:U ratio due to increase of U through digitalis, in patients with hypertension, angina, and atrial fibrillation.

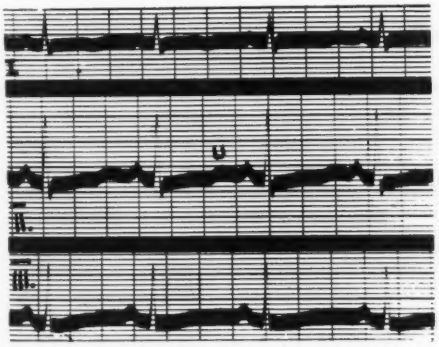


FIG. 12. Abnormal T:U ratio in patient with vertical heart and neurocirculatory asthenia.

measuring the Q-aU distance in V_2 or any other lead with an upright U wave and reporting it to the lead in question; alternately if the position of U is doubtful in all leads, the Q-T distance should be determined; the addition of 0.10 sec. to this will show the approximate position of aU if the rate is between 60 and 80.

What is the diagnostic importance of abnormal U wave in coronary disease? Viewed through critical eyes, I do not believe it is great. In acute cardiac infarction, with so many diagnostic signs, the U-wave changes are unimportant.

In 30 per cent of patients with chronic coronary disease the U waves are normal. In cases with abnormal T:U ratio (28 per cent) or upright U with inverted T (20 per cent) the same factors that influence the R-T changes—left ventricular hypertrophy and digitalis—will make the assessment of the abnormal U wave difficult. Of the remaining 22 per cent, the absence of such an elusive wave as U in 6 per cent can hardly constitute an important diagnostic sign though it calls for an effort test. The U-wave inversion or delay without T-wave changes in the remaining 16 per cent could be regarded as diagnostic if it could not be seen at an advanced age without clinical coronary disease. On the other hand, its appearance during effort test with anginal pain is a pointer toward its coronary origin. The most that can be said is that in the presence of equivocal S-T and T changes or atypical chest pain, an inverted U wave is a useful confirmatory sign of coronary disease.

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Symposium on Coronary Dilator Drugs

By LLOYD L. HEFNER, M.D., BEN FRIEDMAN, M.D., T. JOSEPH REEVES, M.D., E. E. EDDLEMAN, JR., M.D., AND TINSLEY R. HARRISON, M.D.

DR. LLOYD HEFNER: This conference on coronary vasodilator drugs is best begun by presentation of a patient, a 59-year old white male semi-retired lumber dealer. He was first admitted to the University Hospital on September 28, 1955, complaining of chest pain. He had been entirely well until 3 months prior to admission, when after carrying a heavy suitcase about 25 yards, he noted an aching pain in the left side of the neck and a sensation of pressure in the substernal area. Movement of the arms, thorax, or neck had no influence on the pain. There was no associated feeling of dyspnea, faintness, weakness, palpitation, or belching. The pain disappeared within 2 min. after he sat down. Since that time, he has had numerous similar attacks varying only in severity and duration. The pains were precipitated usually by exertion or excitement and relieved by rest and by nitroglycerin. Two episodes of pain occurred at night, each following a nightmare. Two attacks of pain stood out as more severe than the rest. Each struck about 30 min. after the noon meal while at rest, and lasted about 20 min., requiring injections for relief. The first of these occurred 1 week after his first attack. At this time nitroglycerin tablets were prescribed and he was advised to restrict physical activity. The second episode appeared 2 weeks later. At this point, he was confined to bed for a period of 1 month, during which time he was free of chest pain. For the 1 month immediately preceding admission he had been up and about, but only to a very limited extent. In spite of the very mild activity that he permitted himself, he continued to have chest pain, averaging about 1 attack every 2 days. He had never experienced orthopnea, exertional dyspnea, palpitation, or peripheral edema.

The past and personal histories were noncontributory. His right arm was amputated 25 years ago after severe trauma. His mother and 1 brother died of "heart attacks" at the ages of 62 and 42, respectively, and 2 other brothers suffered from angina pectoris.

On admission, he appeared to be a pleasant, calm, intelligent man, who was able to lie comfortably flat in bed. He was not obese. The blood pressure was 130/88, temperature normal, pulse rate 80; respirations 18 per minute. There were no xanthelasmata, no sign of congestive heart failure, cardiac enlargement, murmurs, arrhythmia, or gallop rhythm. The apical impulse was not at all remarkable. There was a mild sclerotic change (grade 2) in the arterioles of the fundi. Except for the absence of the right arm, the remainder of physical examination was normal.

Laboratory studies were all within normal limits. These included glucose tolerance test, complete blood count, sedimentation rate, blood urea nitrogen, cholesterol, and roentgenogram of the chest. The electrocardiographic and kinetocardiographic findings will be presented later.

The patient had 2 attacks of chest pain while he was undergoing his initial examination but thereafter had chest pain only following exer-

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tion. For the first 2 days, exercise under supervision was performed. He was never allowed to continue exercise after pain developed. Thereafter, he walked for 10 min. every hour during the day limited only by the appearance of pain. Increasing exercise tolerance was noted on no additional therapy, so that eventually he was unable to induce angina by walking. He was then started on nitroglycerin ointment, in an initial dose of 1 inch applied to the chest every 4 hours during the day. This dose was gradually increased, until at the time of discharge he was applying 2½ inches of nitroglycerin ointment every 4 hours during the day. On this regimen, he had no further attacks of chest pain.

Are there any questions? Dr. Friedman, I will project a slide of the electrocardiographic findings before and after exercise. Would you discuss them and also the use of exercise tests.

Dr. Ben Friedman: The only striking abnormality in the control record is the inversion of the T wave in lead V_4, and the somewhat flattened T wave in aV_L. Following exercise one notes depression of the S-T segment in lead V_4, accompanied by deepening of the S wave, a slight change in a downward direction of the slope of the S-T segment and inversion in the direction of the T wave. These changes have been regarded by many individuals as definitely positive and diagnostic of coronary insufficiency. The criteria for a positive exercise test vary according to the interpreter. No criteria devised thus far will pick up every patient with coronary disease and at the same time exclude all false positive reactions. As the requirements for a positive test are relaxed to be made more sensitive they become perforce less specific.

The major changes that develop in the electrocardiogram during an attack of angina pectoris, whether induced or spontaneous, consist in depressions in the S-T segment, flattening or inversion of the T wave, and, rarely, in the development of Q waves, various degrees of intraventricular block, and transient ventricular tachycardia. Recent studies have emphasized the significance of changes in the configuration of the S-T segment in a downward sloping direction. A negative exercise test does not exclude the diagnosis of coronary insufficiency.

The factors that produce the abnormal electric activity in the heart are not necessarily the same as those that cause the pain. One may develop independently of the other, and when they occur together very often the electric changes may appear 5 or 10 min. after conclusion of the exercise and subsidence of the pain. The degree of stress sufficient to produce angina pectoris varies enormously from patient to patient. Some subjects experience pain and develop electrocardiographic changes on walking a short distance on level ground. Others have discomfort only after climbing 6 flights of stairs half an hour after a meal, while carrying some ice cubes in each hand. To elicit a positive test it is often necessary to reproduce as far as possible those conditions that prevail at the time the individual has a spontaneous attack. The best end point is pain, unless the development of dyspnea or fatigue terminates the exercise.

Finally, the exercise tests carry some risk; they should not be performed as a diagnostic test if the diagnosis is apparent without them, as is the case in the patient presented here this morning. Fortunately, the diagnosis of angina can be made in the majority of cases by a painstaking history. In a few instances the pain may be bizarre, the history atypical, and there may be a confusing variety of pains from which it is difficult to pick out angina pectoris. In those situations the exercise tests are of inestimable value and, indeed, the diagnosis often cannot be made without them. The point I wish to emphasize is that exercise tests should supplement and not replace the more enlightening although more time-consuming methods, namely the history and physical examination.

Dr. Hefner: Thank you Dr. Friedman. Are there any questions or comments concerning the electrocardiogram in angina pectoris?

Dr. T. Joseph Reeves: Dr. Friedman, will you comment on the effects of digitalis on the electrocardiogram?

Dr. Friedman: Digitalis, even in normal individuals, followed by exercise, can produce changes that are identical to those observed during exercise in a patient with angina pectoris.

Dr. Hefner: Dr. Eddleman, will you begin the discussion of coronary vasodilator drugs?

Dr. E. E. Eddleman, Jr.: The beneficial

effect of nitrites in the treatment of angina pectoris has been attributed to increased coronary blood flow, which has been shown to occur both in systole and in diastole. The pharmacologic action of the nitrites is more complex than just a dilator effect on the coronary vessels. It has been well recognized that nitrites do dilate veins and arterioles. The facial flush is probably due to dilation of the arterioles. In addition, relatively large arteries are dilated, as indicated by the temporal pounding that one often sees clinically.

Studies on changes in cardiac output produced by the nitrite drugs have given variable results. Some have reported an increase and others a decrease; the consensus is that the stroke volume diminishes but the minute volume of cardiac output is not appreciably altered as long as the patient is in the supine position. There is a fall in blood pressure in the upright posture and the cardiac output may similarly decrease in that position. There are other cardiovascular effects of the nitrites that are of interest.

1. The heart's size decreases, the stroke volume diminishes, the minute volume being maintained by the increase in the heart rate.

2. Pulmonary artery pressure increases and in some instances in the experimental animals, it has risen to levels comparable to systemic pressure. This is associated with blanching of the lungs. Therefore, the action of the nitrite on the pulmonary vessels produces constriction rather than dilatation.

3. The cardiac pulsations are increased after the nitrites. This is manifested by an overactive precordium that can easily be detected with the kinetocardiogram or slit kymogram.

In summary, even though there is more than one pharmacologic action of the nitrites, they are undoubtedly our most potent coronary dilators.

DR. HEFNER: Thank you, Dr. Eddleman. Are there any comments?

DR. S. RICHARDSON HILL: Would you comment, Dr. Eddleman, on the use of nitroglycerin in patients with myocardial infarction?

DR. EDDLEMAN: I think the question of the use of nitrites in the presence of myocardial infarction is still unsettled at the present time. The objection has been that a possible fall in blood pressure may lead to extension or to the occurrence of an additional myocardial infarction. Since in the supine position the blood pressure is not significantly affected by small doses, I think that there is some rationale for the use of nitroglycerin in patients with myocardial infarction; however, I do believe that they should be used with caution.

DR. HEFNER: Are there any further comments? Dr. Reeves, will you continue the discussion of the coronary vasodilator drugs and give us some of the clinical applications of these medicines.

DR. REEVES: As Dr. Eddleman has indicated, the most effective coronary vasodilator drug thus far found is nitroglycerin. This is a reflection of the balance between the effect of the vasodilator on cardiac work against its action on coronary flow. Aminophylline and papaverine in appropriate dosage may result in an absolute increase in coronary blood flow that may equal or actually exceed that induced by nitroglycerin. However, these drugs, particularly aminophylline, have a direct effect on the myocardium to increase cardiac output and to increase cardiac work. Consequently, the balance between work and coronary flow is altered in a less favorable way than is the case with nitroglycerin. As pain of angina pectoris itself is characteristically of very brief duration, it is at times very difficult to tell whether or not a particular agent has actually resulted in abbreviation of the duration of that episode. Of considerably greater importance in the clinical usage of the coronary vasodilator drugs is the prevention of pain, and in the enhancement of the exercise tolerance of a given individual with angina pectoris. The brief duration of action of nitroglycerin has led to agents possessing more prolonged effects. Various drugs have been used, including aminophylline, papaverine, the analogues of papaverine and the various long-acting or slowly absorbed nitrite or nitrate preparation. Dr. Russek and his co-workers studied the effect of various preparations on exercise tolerance, as measured by pain response and by prevention of the abnormal changes in the electrocardiogram. With this procedure they were unable to demonstrate a protective action for aminophylline[1] and for

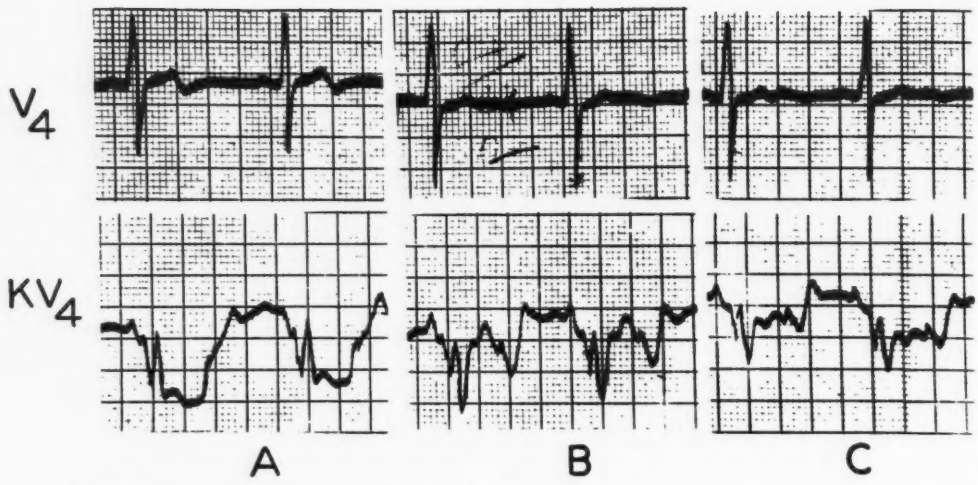

FIG. 1. Simultaneous electrocardiogram and kinetocardiogram at the apex. Tracing *A* is a resting control, showing the normal systolic retraction of the chest wall. Tracing *B* was obtained on the same patient a few minutes later, after he had exercised sufficient to produce slight anginal pain. Note the systolic bulge, most marked in late systole. Tracing *C* was made 30 min. after tracing *B*, during which time the patient had rested. The bulge has partially but not entirely disappeared.

papaverine in doses ordinarily employed. They did note a significant protective effect with pentaerythrol tetranitrate (Peritrate) administered with the stomach empty. This fact possibly explains some of the contradictory findings that have been reported. Other clinical studies in which this factor has not been completely controlled have indicated that Peritrate itself will not significantly reduce the incidence of pain in patients with angina pectoris. Nitroglyn, a preparation of nitroglycerin in sustained-release form, has been studied in a similar fashion by Dr. Russek and his group. They were unable to demonstrate any significant protection afforded by this drug, presumably due to failure of absorption at rapid enough rates. Papaverine, when given in adequate dosage may afford significant protection, but being on the narcotic list and rather expensive it has not been employed widely.

DR. BERRY: What is the duration of the protective action of sublingual nitroglycerin?

DR. REEVES: Objectively, as far as one can tell by protection afforded in exercise tolerance tests, utilizing the electrocardiogram, the duration of action does not extend beyond 30 to 45 min., the average being between 15 and 30 min. On the other hand, many patients are convinced that the duration of protection is between 2 and 3 hours.

DR. HEFNER: At this point it will be appropriate to discuss the kinetocardiographic tracings obtained on the patient presented earlier. The kinetocardiograph is an instrument that measures movements of the chest wall. Figure 1 shows a simultaneous electrocardiogram and kinetocardiogram. Tracing *A* was made while he was resting, and shows the normal systolic retraction of the chest wall beginning early in systole, and maintained throughout systole, and the outward motion occurring at the end of systole, with relaxation of the heart. Tracing *B* was obtained on the same patient a few minutes later, after he had performed a standardized exercise for 1 minute. There is the expected change in the electrocardiographic lead, which is V_4. There is a striking change in the kinetocardiographic tracing, which is also taken in the V_4 position, namely, an outward bulge of the precordium, most marked in late systole. This is an abnormal bulge and has not been found following exercise in normal subjects. Tracing *C* was made 30 min. after tracing *B*, during which time the patient had rested. It is

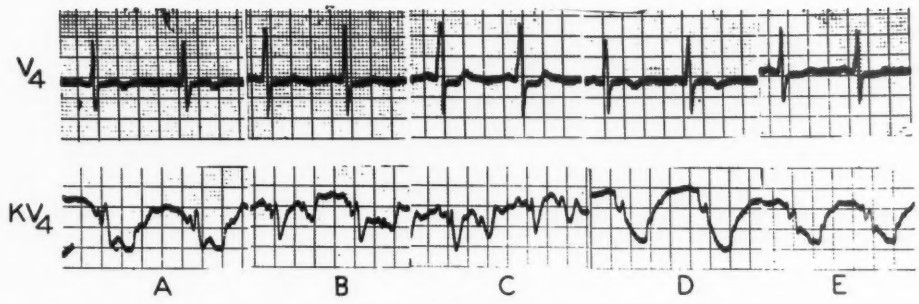

FIG. 2. Simultaneous electrocardiogram and kinetocardiogram at apex. Tracing *A* is a resting control. Tracing *B* was made after 1 minute of exercise. The patient had no pain but the systolic bulge has appeared. Tracing *C* was made a few minutes later; after 10 sec. additional exercise had produced anginal pain. The bulge is still obvious. Tracing *D* was made after 30 min. rest, and is again normal. Tracing *E* was made after the patient was given 1/100 gr. of nitroglycerin sublingually, following which he again performed the same exercise that produced both pain and a systolic bulge in tracings *B* and *C*. No pain and no bulge appeared.

obvious that the bulge has partially but not entirely disappeared.

Figure 2 again demonstrates a simultaneous electrocardiogram and kinetocardiogram at the V_4 position. This figure is designed to show the effects of oral nitroglycerin. Tracing *A* was made as a control with the patient at rest, and again one sees the normal retraction of the V_4 precordium throughout systole. Tracing *B* was made immediately after 1 minute of the standard exercise, and again the systolic bulge appeared. At this time the patient had no pain, but 3 min. later, after about 10 sec. of additional exercise, he developed typical anginal pain and the bulge was still obvious. Tracing *D* was made after the patient had rested about 30 min. and again shows a normal tracing in the kinetocardiogram in the V_4 position. Tracing *E* was made after the subject was given 1/100 gr. of nitroglycerin sublingually, following which he again performed the same exercise that produced both the pain and the systolic bulge in tracing *C*. As you can see, after premedication with sublingual nitroglycerin, he had no pain and the systolic bulge did not develop.

Figure 3 is designed to demonstrate the effectiveness as well as the duration of action of nitroglycerin ointment. Tracing *A* is the control tracing with the patient at rest. Tracing *B* was made after 1 min. of standard exercise. A tremendous systolic bulge is obvious in the kinetocardiogram. The patient, however, experienced no anginal pain at this time. The patient was then given an application of 2 inches of nitroglycerin ointment to the chest, and at intervals over the succeeding 3½ hours other tracings were made, each immediately after the same standard exercise. Tracing *C* was recorded one half hour after the application of the nitroglycerin ointment. There was no pain but, as you can see, the systolic bulge was still present, although with not as great amplitude as in tracing *B*. Tracing *D* was made 1 hour following the application of the nitroglycerin ointment. One can hardly say there was a bulge but there was certainly failure of systolic retraction as compared to the normal tracing *A*. Tracing *E* was taken at 2 hours. There was no pain and no systolic bulge was demonstrated. Tracing *F* was made 2½ hours after the application of the nitrol. Again, the tracings were normal and the patient had no pain. Tracing *G* recorded at 3 hours showed again no bulge and the patient had no pain. Tracing *H* was made at 3½ hours after the application of the nitrol ointment. At this time the patient had mild anginal pain. The reappearance of the bulge is apparent.

Are there any questions?

Dr. Harrison, will you conclude the discussion, and please discuss these tracings, too?

DR. TINSLEY R. HARRISON: There is 1 point that should be emphasized. This man had been taking practically no physical exercise. He had

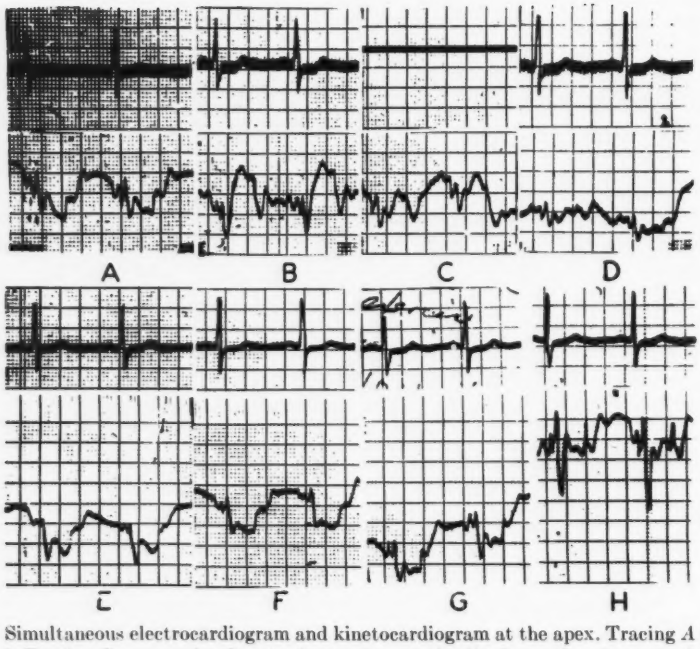

FIG. 3. Simultaneous electrocardiogram and kinetocardiogram at the apex. Tracing *A* is the resting control. Tracing *B* was made after 1 minute of a standardized exercise. A tremendous systolic bulge is present, but the patient had no pain. The patient was then given an application of 2 inches of 2 per cent nitroglycerin ointment to the chest, and the succeeding tracings were made at intervals thereafter, each immediately after the same standardized exercise. Tracing *C* was recorded ½ hour after the application of the ointment. The exercise produced no pain but the bulge is still present, though less marked. Tracing *D* was made 1 hour after the ointment. The presence of a bulge is questionable. Tracing *E*, 2 hours after the ointment, demonstrates no bulge, and the patient had no pain. Tracing *F*, 2½ hours and *G* 3 hours after the ointment, reveal normal tracings, and the patient had no pain. Tracing *H* at 3½ hours after the ointment shows that the bulge is beginning to reappear. The patient had mild anginal pain at this time.

been having pain at home and during the past few days in the hospital, on very slight effort—walking a couple of hundred feet or less. On no therapy other than being encouraged to walk every hour, the severity and frequency of pain diminished sharply, and the amount of exercise required to induce it increased markedly. This is analogous to the individual who has his pain on the first hole of the golf course, and plays the remaining 18 holes with no further discomfort. The evidence that mild physical exercise, not sufficient to induce pain, is not harmful but is positively beneficial, is in my opinion becoming stronger each year. If a patient repeatedly undertakes subthreshold exercise, it is not long before the amount of exercise required to induce the pain is increased. This is not true in every patient, but it is true in a large percentage of them. I have been interested in coronary dilator drugs for about 30 years, and all of them, in my experience, have been disappointing except the nitrites. The long-acting nitrites such as erythrol tetranitrite, pentaerythrol tetranitrate (Peritrate), have occasionally seemed to have a striking effect, but much more commonly the results have been disappointing.

Some years ago, having read a paper in one of the Scandinavian journals describing the use of nitroglycerin ointment locally for intermittent claudication, we tried it on a patient who happened to have both intermittent claudication and angina pectoris. Before medication, this patient developed leg pain and chest pain about the same time, with walking. Rather to our surprise, after application of nitrol ointment the patient had no improvement in the leg pain on walking, but his chest pain disap-

peared. This was the beginning of my interest in the use of this ointment. We have now tried it in more than 20 patients, who have been well controlled, and in most of them one could demonstrate benefit. Thus, during a period beginning about 30 to 60 min. after application of the ointment and extending up to 2 to 4 hours the amount of effort required to induce chest pain has usually been definitely increased. Of the various long-acting nitrites, this is the only one that in my experience has been effective in a large percentage of patients.

More than 20 years ago Wiggers and Tennant showed that when one ligated a coronary artery of a dog, within a matter of a few beats there was a bulge in the ischemic area,[2] which, of course, is due to failure of contraction of that part. It has long been known that people who have had a myocardial infarction may show a ventricular aneurysm at autopsy, and under certain circumstances a ventricular aneurysm may be detected during life. Dr. Myron Prinzmetal pointed out to me, when he was here last year, that in the studies he and his colleagues had made on the dog's heart they could find 2 different types of bulges, which he called the "late systolic bulge" and the "early systolic bulge." In his dogs it appears that moderate degrees of ischemia tended to cause the late systolic bulge. Our experience in human subjects has been similar. We have had a number of other patients who exhibited a precordial bulge during anginal attacks. This is by no means true in every patient with angina pectoris. We assume that if the bulge is downward or posterior we cannot detect it at present but if it happens to involve the septal region or the apex, we often detect it. From a physiologic standpoint, the demonstration that a person may have a temporary ventricular aneurysm, if you want to call it that, is of interest. Most of the people with anginal attacks who have shown a bulge have shown it during the early part of ejection, i.e., the bulge starts in midsystole. Individuals who have had ventricular aneurysms after myocardial infarctions have shown the bulge very early in systole, beginning within .02 to .04 sec. after the onset of the ventricular complex in the electrocardiogram. In other words, if all the muscle is destroyed, the slightest rise in pressure in the ventricle produces this bulge. If the muscle is still living but nevertheless is ischemic a greater rise in intraventricular pressure is required to produce the bulge. At times it has been possible to localize the infarct by simple palpation. Studies such as this one seem to indicate that under certain conditions the nitrite group of drugs helps not only the pain but also the physiologic mechanism of the disease. I do not see how one can escape such a conclusion when one sees evidence such as Dr. Hefner has presented.

That brings us to the question of the role of nitrites in the treatment of coronary artery disease. I may say in answer to Dr. Hill's question about the use of nitroglycerin in myocardial infarction, that I do not believe anyone really knows. We have very cautiously given it to a large number of patients, and all I can say with certainty is that we have never seen harm from it. The initial dose has usually been 1/400 gr. every 2 hours. The blood pressure is observed carefully and if a significant decline occurs, which is rare so long as the patient remains recumbent, dosage is decreased. Otherwise, dosage is gradually increased to about 1/200 gr. every hour. In a few instances favorable electrocardiographic changes have been demonstrated. In the majority of cases there has been no obvious objective change, and we cannot say with certainty that the patient was benefited. We can say, I think, that no patient has been hurt.

Insofar as the use of nitroglycerin in angina pectoris is concerned, we have a different situation. I think there is no question whatever about the benefit of the combination of subthreshold exercise, plus repeated use of coronary vasodilator drugs—nitroglycerin for quick effect, and the nitrol ointment for a prolonged effect. We have enough objective data to indicate that this is a method of treatment that helps the disease as well as the symptoms.

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CLINICAL PROGRESS

Procaine Amide

A Review

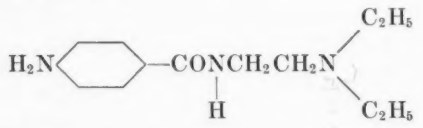
By HERBERT J. KAYDEN, M.D., B. B. BRODIE, PH.D., AND J. MURRAY STEELE, M.D.

PROCAINE amide was introduced for the treatment of cardiac arrhythmias 6 years ago. Since then a number of studies with the compound have been reported. A review of the results may help in appraising the value of the drug as a therapeutic agent.

The first step toward the development of procaine amide was taken when Mautz,[1] in 1936, showed that procaine, applied directly to the myocardium of animals, elevated the threshold of ventricular muscle to electric stimulation. Beck and Mautz[2] then demonstrated that the topical application of procaine in surgery involving stripping of the pericardium, reduced the occurrence of ventricular and atrial extrasystoles. In 1946, Burstein[3] reported that procaine was an effective antiarrhythmic agent when injected intravenously, and he employed it in anesthetized patients prophylactically as well as therapeutically. Although of undoubted effective antiarrhythmic activity, procaine has limited use in the general treatment of arrhythmias because of its central stimulatory effects, which restrict its use to anesthetized patients.

A study on the fate of procaine in man showed that the drug after intravenous injection was enzymatically hydrolyzed in plasma with extreme rapidity to para-aminobenzoic acid and diethylaminoethanol.[4] The rapid hydrolysis of procaine suggested that its antiarrhythmic action might be mediated through one of the metabolites. Para-aminobenzoic acid was found to have no antiarrhythmic activity but diethylaminoethanol in large dosage protected dogs against arrhythmias induced by cyclopropane and epinephrine and was effective in patients with ventricular tachycardia.[5] A number of other dialkylamino alcohols closely related in structure to diethylaminoethanol were shown to be ineffective as antiarrhythmic agents in nontoxic doses.[6]

Although diethylaminoethanol had undoubted antiarrhythmic action, the large doses required in man indicated that the action of procaine was not mediated through this metabolite, and the hypotension resulting from its use made the compound undesirable as a therapeutic agent. The striking observation, however, that the compound was effective in doses that had minimal central stimulatory effects stimulated a search for a drug having the potency of procaine but lacking its central stimulatory action. A number of derivatives of diethylaminoethanol were synthesized.* The compounds were screened in dogs for their efficacy in protecting against ventricular tachycardia induced by cyclopropane and epinephrine. The most potent compound among these studied was procaine amide (p-amino-N-((2-diethylaminoethyl))benzamide),[7] a substance in which the ester linkage of procaine is replaced by an amide linkage.



Numerous studies indicate that the pharmacologic actions of procaine amide are similar to those of procaine, but that the amide is

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* Synthesized by Dr. William Lott—E. R. Squibb & Co., New Brunswick, N. J.

considerably more stable in the body and exerts antiarrhythmic action in doses having little effect on the central nervous system.[8]

Physiologic Disposition and Fate of Procaine Amide

Knowledge of the fate and physiologic disposition of a drug in man is helpful in establishing the optimal mode of administration. Procaine amide is rapidly and virtually completely absorbed from the gastrointestinal tract and the peak plasma level of the drug is achieved usually within 2 hours after oral administration.[8] After intramuscular administration, maximal plasma levels are obtained within 1 hour.[9] Following its absorption, the plasma levels of the drug decline at a rate of only 10 to 15 per cent per hour. About 60 per cent of the drug is excreted unchanged in the urine and about 5 per cent as free, or conjugated para-aminobenzoic acid. The relative stability of the drug, compared to procaine, is due to the fact that plasma esterase, which catalyses the hydrolysis of procaine, does not act upon procaine amide.

At plasma levels of 10 to 20 mg./L. (levels within the range of therapeutic concentration) only about 15 per cent of the drug is bound to plasma proteins; but considerable amounts are reversibly bound to various organ tissues, especially liver, spleen, lung, and heart.[8] This explains, in part, the relatively slow decline in plasma levels, since tissue depots of drug serve as a reservoir as the compound is lost by excretion or metabolic transformation.

The drug does not accumulate on repeated oral dosage. Thus, on a dosage schedule of 750 mg. every 6 hours, the peak plasma level is achieved within 24 hours. Patients with renal damage or with congestive heart failure excrete procaine amide more slowly than do normal persons and cumulative effects are consequently more likely in such individuals.

Pharmacology

Animal. Procaine amide exerts many actions on the heart and the circulation. Its most important effects are similar to those of quinidine.[10, 11] Conduction of cardiac muscle is slowed, though to a different degree, in atrium, ventricle, and the bundle of His. The effect is greatest across the A-V node, suggesting the greater sensitivity of this tissue to the drug.[12] The refractory period is prolonged with the atrium being much more affected than the ventricle. Contractility of the heart is usually not affected by procaine amide, in contrast to the depressant action of quinidine.[10] Excitability of both the ventricle and the atrium to electric stimulation is profoundly depressed.[11, 13, 14] This can be demonstrated during most of the cardiac cycle and is more marked in the ventricle than in the atrium. The depression of excitability is roughly correlated with plasma levels of the drug. The drug also possesses anticholinergic properties, since high doses sometimes accelerate the heart rate. Larger doses may cause atrioventricular block inducing ventricular extrasystoles and even lead to ventricular fibrillation.[8]

Procaine amide has been shown to be effective in protecting against ventricular tachycardia induced by the classical technic of Meek,[15] which involves an injection of epinephrine in dogs under cyclopropane anesthesia.[8] It also suppresses ventricular tachycardia produced by ligation of coronary arteries in the dog.[16, 17] This experimental preparation attempts to simulate the human arrhythmia, and provides a stable unanesthetized experimental animal for 20 to 72 hours.

There have been several experimental studies on the effects of procaine amide in digitalis-intoxicated animals.[18-20] Goldberg and Cotten[18] produced ventricular tachycardia in 14 dogs with digitoxin or ouabain and reverted 8 of the animals to normal sinus rhythm with intravenous procaine amide. In the 6 other animals, procaine amide produced slow idioventricular rhythms, followed in 4 animals by cardiac arrest. These authors also reported that procaine amide did not increase the lethal dose of ouabain in cats. Mosey and Tyler[19] found that procaine amide reverted the ventricular tachycardia produced with ouabain in 7 of 8 dogs.

Zapata Diaz, and co-workers[20] also stressed

the fact that procaine amide might eliminate ventricular extrasystoles and ventricular tachycardia caused by digitalis. Their work also indicated that the drug might also initiate ventricular fibrillation since, in their dogs, procaine amide increased the delay in intraventricular conduction originally caused by digitalis. These additional toxic effects occurred only after doses of procaine amide (150–325 mg./Kg.) considerably higher than the therapeutic doses used in man.

The ganglionic-blocking properties of procaine amide were studied by Paton and Thompson[21] in the superior cervical ganglion of the cat. Their observations indicated that procaine amide not only antagonizes the effects of acetylcholine, but inhibits its release at the ganglion.

The actions of procaine amide on the central nervous system are not prominent, but a large dose rapidly injected in dogs will cause tremors.[8] Procaine amide has local anesthetic activity comparable to procaine, but it is not very effective for blockade of nerve trunks.[10]

Man. Studies of the electrocardiographic effects have shown prolongation of the P-R, QRS, and Q-T intervals, indicating a delayed rate of conduction in atrium and A-V node, a delay in intraventricular conduction, and a prolongation of the refractory period.[22] These actions are potentially dangerous if the dose of drug is too high or if it is administered too rapidly. They are discussed further in the section on toxicity and include the production of extrasystoles, atrial and ventricular fibrillation, and cardiac standstill. Physiologic measurements have shown a decrease in cardiac output, peripheral blood pressure, and pulmonary arterial pressure during a single intravenous injection.[22] The hypotension induced by slow intravenous injection (50 mg./min.) of procaine amide is slight but in individuals who already have a lowered blood pressure because of an arrhythmia or diseased myocardium, the decline may be profound. The effect on blood pressure is less marked when the drug is injected intramuscularly and is usually absent following oral administration. A number of these phenomena may have a role in the therapeutic action of procaine amide, but the exact mechanisms are still obscure.

The clinical reports on the use of procaine amide in patients who have developed rhythmic disturbances due to excessive dosage with digitalis are not in entire agreement.[23-30] In our experience, it has been a useful agent in correcting these abnormalities, although 1 patient who received only 145 mg. of procaine amide intravenously directly after an intravenous dose of lanatoside-C developed ventricular fibrillation, possibly due to the procaine amide. Other groups also recommend using procaine amide as a therapeutic agent in the treatment of arrhythmias caused by excessive digitalis dosage.[27-30] However, in view of the experimental work of Zapata's group procaine amide should probably be used cautiously when a digitalis compound has been administered.

Effects on Various Arrhythmias in Man

In reviewing reports on the efficacy of procaine amide in the various arrhythmias,[31-68] it was noted that some authors described results in terms of success, partial success, and failure, while others recorded only success and failure. Partial success, in some cases, referred only to slowing of the aberrant rhythm without reestablishment of the normal, in other cases to incomplete abolition of ectopic foci, and in still others to a temporary correction of the abnormal rhythms. In calculating per cent success for table 1, partial success has been regarded as failure.

Table 1 presents the results obtained with procaine amide in various arrhythmias, but a few comments may be made to emphasize certain observations. It is noteworthy that almost 9 out of 10 cases of ventricular premature contractions responded favorably to procaine amide. The results of the treatment of 100 instances of ventricular tachycardia are particularly striking—78 complete successes and 7 additional instances with partial success. Of further interest are the frequent reports that procaine amide is effective in maintenance therapy, preventing recurrent bouts of ven-

TABLE 1.—*Summary of All Arrhythmias Treated with Procaine Amide*

Rhythm	References*	No. of patients	Success	Partial success	Failure	% Success
Atrial premature contraction	32, 34, 58, 36, 35, 33	13	8		5	52
Paroxysmal atrial tachycardia	24, 41, 34, 9, 36, 35	40	28	7	5	70
Atrial flutter (acute and chronic)	25, 41, 39, 34, 58, 36, 9, 33, 21, 32, 35, 12	53	7		46	13
Recent atrial fibrillation (less than 2 wks.)	34, 33, 36, 25, 32, 37	42	37		5	88
Chronic atrial fibrillation (more than 2 wks.)	34, 32, 25, 33, 9, 37, 35, 36, 41, 71, 12, 58, 21	155	33		122	21
Supraventricular tachycardia	40, 33, 58, 9, 52	14	10		4	66
Nodal tachycardia	38, 41, 34, 9, 71, 26, 53, 32, 36	26	20		6	74
Ventricular premature contractions	26, 41, 37, 9, 58, 32, 71, 21	185	162	5	18	88
Ventricular tachycardia	38, 26, 41, 37, 71, 24, 48, 32, 9, 68, 12, 58, 60, 45, 62, 66, 46, 47, 49	100	78	7	15	78

* Listed in decreasing order of total number of cases treated in each arrhythmia.

tricular tachycardia as well as other paroxysmal arrhythmias.

When the atrial arrhythmias are considered, it becomes apparent that in recently developed atrial fibrillation (2 weeks or less), there is a high degree of success (88 per cent) in contrast to long-standing atrial fibrillation, in which only a fifth can be converted to normal sinus rhythm. By far the bulk of the group with atrial flutter were individuals with a long history of this arrhythmia, and the successful conversion percentage was very small—13 per cent. Thus, duration of the aberrant rhythm is apparently of considerable importance in determining the chances of successful therapy.

The per cent of successful cases might have been higher if the dose used in most studies had not been a predetermined arbitrary one. Often treatment was discontinued before either toxicity or a satisfactory therapeutic response had occurred. This was particularly true when the drug was given orally, but was also noted in intravenous therapy when the original suggestion that no more than 1 Gm. at a time be given was followed too literally. Subsequent observations[38] have shown that higher doses up to 2½ Gm. at a single injection may be necessary to achieve reversion to normal rhythm.

The developments during the last 10 years in anesthesia and surgery have markedly increased the number of intrathoracic surgical operations. Although arrhythmias may occur during abdominal surgical procedure, they are much more frequently observed during pulmonary and cardiac surgery. The anesthetist is usually charged with supervising the clinical status of the patient during surgery and has frequent opportunities to observe and treat cardiac arrhythmias.[54] In many hospitals, there is constant monitoring, by an oscilloscope or some other means, of the electrocardiogram during all intrathoracic surgery. The incidence of rhythmic alterations, which include occasional extrasystoles, ventricular tachycardia, and cardiac arrest, is difficult to evaluate because of incomplete reporting. Prophylactic administration of procaine amide for intrathoracic and, particularly, for cardiac surgery has been recommended but it would appear that protection against mechanical stimulation is difficult, if not impossible, to achieve. When used therapeutically for an established arrhythmia during anesthesia, procaine amide has been reported to be effective.[54] During cardiac catheterization, the arrhythmias induced by mechanical stimulation appear slightly if at all affected by procaine amide.[55]

To obtain relatively bloodless fields in neuro- and ophthalmic surgery, anesthetists have been lowering blood pressure by using the ganglionic-blocking agent, hexamethonium bromide.[56, 57] British workers have reported that hexamethonium alone was successful in only about 60 per cent of cases and that tachycardia associated with the use of hexamethonium was

frequently responsible for the failure to obtain satisfactory hypotension. Procaine amide was tried in conjunction with hexamethonium in the hope that it would afford protection against tachycardia. Reports indicate that it potentiates the hypotensive action of hexamethonium, reducing the required dose of this drug by about a third and increasing successful cases by about 25 per cent.[23, 56, 57]

Dosage and Routes of Administration

A variety of dosage schedules have been employed in treating cardiac arrhythmias. When procaine amide is administered intravenously, the rate of injection appears to be as important as the total dose. The use of electrocardiographic control and frequent recordings of blood pressure are essential for safety when procaine amide is given intravenously, but when administered slowly (50–75 mg./min.), as much as 3 Gm. has been given[38] without untoward effects. It is well to stress that in the absence of hypotension and electrocardiographic abnormalities produced by the drug, it may be given until the desired effect is achieved, but intravenous administration entails certain dangers because of sudden development of cardiac abnormalities. The intramuscular route provides greater safety and single doses of 0.5 to 1 Gm. at repeated intervals have been satisfactory.[58] The intravenous route should be reserved for those patients whose desperate condition requires immediate therapy.

The oral dose of procaine amide required to revert any particular arrhythmia is variable. An initial dose of 1 Gm. followed by 0.5 to 1 Gm. doses every 3 to 4 hours is adequate for many patients, but the total daily dose may reach 10 Gm. to revert an arrhythmia or provide prophylaxis against recurrences. The usual effective dose is about 3 to 6 Gm./day, but if the desired effect has not been achieved after 48 hours, the dose should be increased, either by increasing the frequency or increasing the individual dose, since a stable plasma level is reached after 24 to 48 hours. Toxic effects, such as nausea and gastrointestinal irritation on 5 Gm. a day may occasionally be so pronounced as to prevent further administration, but many patients take this dose without any difficulty.[59]

Toxicity

Early reports on procaine amide indicated that toxic reactions occurred involving the circulatory, gastrointestinal, and central nervous system. Subsequent reports have included these and a number of other complications. The electrocardiogram is frequently altered, but the prolongation in the P-R, QRS, or Q-T intervals need not necessarily be regarded as toxic manifestations, but rather as manifestations of effects on cardiac muscle essential to the action of the drug. However, toxicity can occur due to excessive effects on conductivity and refractory period. As conductivity and refractory period are prolonged, the depressant action on ectopic foci may be inadequate and ventricular extrasystoles, ventricular tachycardia, and even ventricular fibrillation may occur.[60-64] This may be due to local changes (excitability versus depression) in areas of ventricular muscle and the establishment of dominance by 1 focus. In some cases, the apparent induced ventricular arrhythmia is more likely due to aberrant conduction through the ventricular muscle from the supraventricular pacemaker, but electrocardiographic differentiation is frequently impossible in the absence of esophageal recording. During treatment of 7 cases of atrial flutter and 1 of atrial tachycardia, the development of rapid ventricular response to supraventricular pacemaker (1:1 response) was noted. The occurrence of cardiac standstill has been reported,[65-68] and this is a hazard in the treatment of ventricular tachycardia. The depressant effects of procaine amide may be as marked on the basic pacemaker of the heart as on the ectopic focus, and cardiac standstill may follow the cessation of abnormal rhythms.

There exists also 1 clear contraindication to use of the drug, namely atrioventricular dissociation with Stokes-Adams syncope.[69, 70] When administered to individuals with this condition, the basic pacemaker is slowed, allowing ectopic foci to be discharged with the resultant increase in aberrant ventricular activity and development of ventricular

tachycardia, fibrillation, and death. These effects have been noted on both oral and parenteral administration.

Falls in blood pressure during intravenous administration have occurred in a number of patients, mostly those already suffering from some degree of hypotension with ventricular tachycardia. In these latter cases, arterial pressure has usually risen promptly upon the establishment of a normal rhythm. Some authors have recommended the use of vasopressor agents concurrently with procaine amide.[71] It is well to recognize that these agents can produce ventricular arrhythmias, but we have managed to control hypotension using methoxamine, mephentermine, and l-norepinephrine.

Although procaine amide is usually well tolerated, anorexia, nausea, and vomiting have been noted on oral administration, especially with high doses. Flushing and a peculiar metallic taste have occurred on intravenous administration. Chills and fever[72, 73] and drug rash have been reported occasionally.[74, 75] The development of agranulocytosis has been reported in 4 instances.[76, 77] Since periodic blood counts so frequently fail to coincide with the development of agranulocytosis, patients on maintenance oral therapy should be told to report at once any fever, sore throat, or any unusual symptoms of lassitude. As yet, no reports have appeared of purpura or of platelet destruction. In regard to the central nervous system, confusion and hallucinations (both auditory and visual) have been noted, especially in older individuals. Since a considerable fraction of procaine amide is excreted unchanged, individuals with impaired renal function may achieve unusually high concentrations on ordinary doses, an observation that may explain widely variable maintenance doses required by individuals suffering from congestive heart failure.

Relation to Quinidine

Some observers have suggested that procaine amide can be substituted for quinidine in treatment of cardiac arrhythmias. In the light of the limited experience with procaine amide, this would appear unwise and premature. Quinidine has had extensive use for the past 30 years and it will be many years before an equivalent experience can be gained with procaine amide. Many reports have stressed that the particular arrhythmia being treated was refractory to therapy with quinidine but subsequently responded to procaine amide. The reverse has also been reported, particularly in the management of supraventricular arrhythmias, and there are some instances in which both are effective. Some writers have suggested that a mathematic relationship exists between the effective dose of quinidine and of procaine amide, in the ratio of 1:3 or 1:4.[78] While this may be true in the maintenance dose of a particular patient, there is a wide range of dosage response of both drugs in the many arrhythmias studied and failure to respond to very large doses of quinidine does not mean that a large amount of procaine amide will be required for reversion, and vice versa. The pharmacologic and physiologic studies have shown similar qualitative effects but the quantitative differences that exist may explain differences in effectiveness of these 2 drugs. It appears that it is safer to give procaine amide than quinidine intravenously. When it is obligatory to use this route of administration, procaine amide may well be the first choice.

Major Uses

Articles published during these 6 years suggest that procaine amide is an effective antiarrhythmic agent whose major uses appear at present to be as follows: 1. For the management of ventricular premature contractions whether due to intrinsic heart disease, digitalis toxicity, or unknown cause. 2. In the management of ventricular tachycardia, particularly when it is desired to use an intravenous agent. 3. For the treatment of nodal arrhythmias and recent atrial arrhythmias. 4. During the course of myocardial infarction as a prophylaxis against ventricular tachycardia and fibrillation, once ventricular premature contractions are observed. The authors do not recommend its use routinely as a prophylactic agent in surgery or cardiac catheterization, since the

drug does not appear to exert much control over extrasystoles due to mechanical stimuli.

That this compound was found, suggests that other compounds with these pharmacologic properties exist, some perhaps even more potent and less toxic than procaine amide. Certainly, a further search is warranted.

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Jensen, K. B.: A Paper-Chromatographic and Fluorimetric Method for Determining the Cardiac Glycosides and Aglycones of Digitalis Purpurea. Acta pharmacol. et toxicol. **12:** 27 (May), 1956.

A method for determining the cardiac glycosides in digitalis leaves has been devised for determining the individual components in mixtures of pure glycosides and aglycones. Stability tests with tincture of digitalis leaves showed that within 1 year, no other changes occurred than a limited transformation of unknown to known glycosides. The accuracy of the method was assessed on the basis of recovery of the following substances: digitoxin, gitoxin, purpureaglycosides A and B, digitalinum verum, digitoxigen, and gitoxigenin.

AVIADO

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

The Biologic Effects of Tobacco: With emphasis on the clinical and experimental aspects. Edited by *Ernest R. Wynder*. Boston, Little, Brown and Company, 1955, 196 pages. $5.00.

A Primer of Electrocardiography. Ed. 3. *George E. Burch and Travis Winsor*. Philadelphia, Lea and Febiger, 1955, 286 pages, 281 illustrations. $5.00.

Kreislaufregulation. *H. Reindell, E. Schildge, H. Klepzig, H. W. Kirchoff*. Stuttgart, Georg Thieme, 1955, 315 pages, 69 figures. $9.40. (U. S. distributors: Intercont. Med. Book Corp. 381 Fourth Avenue, New York)

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Clinical Hematology. *Maxwell M. Wintrobe.* Ed. 4. Philadelphia, Lea and Febiger, 1956, 1184 pages, 236 illustrations, 20 plates, 18 in color. $15.00.

Interne Therapie der organischen Herz- und Kreislauferkrankungen. Published by Vereinigung der Bad Nauheimer Ärzte. Darmstadt, Dietrich Steinkopff, 1956, 130 pages, 26 illustrations, 8 tables. DM 13. (Available through Intercont. Med. Book Corp., 381 Fourth Ave., New York)

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Collagen Diseases. *John H. Talbott and R. Moleres Ferrandis.* New York, Grune and Stratton, Inc., 1956, 256 pages, 46 illustrations, 16 color plates. $6.50.

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Paris, Expansion scientifique Francaise, 1956, 190 pages, 66 figures. 3.700 fr. (Available through Intercont. Med. Book Corp., New York)

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Treatment of Migraine. *John R. Graham.* Boston, Little, Brown and Company, 1956, 149 pages. $4.00.

Atlas d'électrocardiographie, avec des notions de vectocardiographie. *V. Fattorusso and O. Ritter,* Paris, Masson et Cie, 1956, 296 pages, 291 figures. 3.200 fr. (Available through Intercont. Med. Book Corp., New York)

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The Recovery Room—Immediate Postoperative Management. *Max S. Sadove and James H. Cross.* Philadelphia, W. B. Saunders Company, 1956, 597 pages. $12.00.

Treatment of Heart Disease. *Harry Gross and Abraham Jezer.* Philadelphia, W. B. Saunders Company, 1956, 549 pages. $13.00.

Atti della società italiana di cardiologia. XVII Congress, 1955. Rome, Segreteria della Società, 1956, 418 pages.

Roentgen Signs in Clinical Diagnosis. *Isadore Meschan, with the assistance of R. M. F. Farrer-Meschan*) Philadelphia, W. B. Saunders Company, 1956, 1058 pages, 2216 illustrations. $20.00.

Die Lehre vom allergiekranken Menschen. *Georg Schwöbel.* Bern, Hans Huber, 1956, 158 pages. $4.20 (U. S. distributors: Intercont. Med. Book Corp., 381 Fourth Ave., New York)

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Dermatology. *Donald M. Pillsbury, Walter B. Shelley, and Albert M. Kligman.* Philadelphia, W. B. Saunders Company, 1956, 1331 pages, 564 figures. $20.00.

New Bases of Electrocardiography. *Demetrio Sodi-Pollares, with the collaboration of Royall M. Calder, Editor, English translation.* St. Louis, The C. V. Mosby Company, 1956, 772 pages, 523 figures. $18.50.

The Pathology and Surgery of the Veins of the Lower Limb. *Harold Dodd, and Frank B. Cockett.* Edinburgh and London, E. and S. Livingstone, Ltd., 1956, 462 pages, 313 figures. $12.50.

Elektrophysiologie der Herzmuskelfaser. *Edited by Silvio Weidmann,* Bern, Hans Huber, 1956, 100 pages, 33 figures. $3.90 (U. S. Distributors: Intercont. Med. Book Corp., 381 Fourth Ave., New York)

Clinical Recognition and Management of Disturbances of Fluid Balance. Ed. 2. *John H. Bland.* Philadelphia, W. B. Saunders Company, 1956, 522 pages, 109 figures. $11.50.

Cardiac Pressures and Pulses. A manual of right and left heart catheterization. *Aldo A. Luisada and Chi Kong Liu.* New York, Grune and Stratton, Inc. 1956, 126 pages, 51 illustrations. $6.00.

BOOK REVIEWS

Die Thromboembolischen Erkrankugen und ihre Behandlung. *T. H. Noegeli, P. Matis, R. Gross, H. Runge, H. Sachs (Nine Contributors).* Preface by Irving S. Wright. Stuttgart, Friedrich-Karl Schattauer Verlag, 1955, 623 pages, 228 figures and tables. D.M. 96.

This book summarizes the observations and conclusions of a group of 14 expert contributors who

discuss the thromboembolic complications occurring in their own fields. The etiology, diagnosis and treatment of thrombus formation in different organs and systems are reviewed in six chapters (in peripheral vessels or associated with peripheral vascular diseases, in lung diseases, skin diseases, myocardial infarction, thromboemboli occurring in the abdomen, in the central nervous system or in gynecological and obstetrical diseases). The chapters on myocardial infarction and pulmonary embolism are particularly well developed and documented by appropriate Electrocardiograms and x-ray films. Unfortunately retinal thrombosis and the indication of anticoagulant treatment in certain types of cerebral vascular accidents, i.e., embolism and thrombosis, are not discussed.

The chapter on the physiology of hemostasis and, especially, blood clotting is written with discrimination and presents clearly the sometimes confusing ideas on clotting mechanism. One wonders about some details such as the claimed identity of Factor X (Koller) and P.T.A. (Rosenthal). The nebulous differentiation between "thrombophlebitis" and "phlebothrombosis" in the anatomic pathologic description has finally been abandoned and it is hoped that the practitioner will no longer be lulled into a false security in the presence of "thrombophlebitis" (versus phlebothrombosis). The chapter on blood clotting technics is concise and practical. A short discussion on the value and clinical interpretation of the results of these tests would be helpful (for instance, the heparin tolerance test).

The present indications for surgery in the prevention and treatment of thromboembolic complications are objectively discussed with recognition of limitations of this approach. Particularly interesting is the condemnation of inferior vena cava ligation. On the other hand it is hoped that in the next edition of this book the discussion of the value of homografts will be extended.

The rather long chapter devoted to meteorologic influence on the frequency of thromboembolic accidents is confusing and not of great assistance to the reader.

This up to date, fundamental and well organized book is probably the most comprehensive approach to the study and presentation of the pathogenesis, diagnosis and treatment of thromboemboli that has yet been published. Many references follow each chapter and include the European as well as the recent American literature. Unfortunately, the titles of the articles are not given.

The dangers of every book written by a group of authors are a partial overlapping of the subjects, differences of concepts and lack of a uniform terminology. It can be stated that these inconveniences occur at a minimum in this work. There are certain minor omissions in this monumental work which will undoubtedly be corrected in subsequent editions.

The book is nicely printed and numerous clear illustrations and tables are helpful. It is an authoritative source for specialists in the field but it is too detailed to orient the beginner in this field.

MARC VERSTRAETE

High Blood Pressure. *George White Pickering.* New York, Grune and Stratton, Inc., 1955. 547 pages, 106 illustrations. $9.50.

Professor Pickering presents a delightfully provocative review of hypertension in this book. Anyone familiar with Doctor Pickering's recent writings will be familiar with the general theme of the book but in a work of this size he has presented his concept in detail, together with the material leading him to this conclusion. The book, therefore, is not the usual type of text published. It is primarily an extensive scientific report in which the author reviews previous concepts, presents his own findings and draws his own conclusions. It is not a rewrite of old material in "fresh" form. It is Doctor Pickering's book.

Although the author has not done it, one may divide the book into three parts. In the first an historical review and critique of measurements of blood pressure are presented. A chapter follows on factors affecting arterial pressure, such as diurnal variations, sleep and posture. Then the physiologic aspects of arterial pressure are presented in reasonably good detail. Experimental hypertension is then reviewed and a classification of hypertension is presented. There is no correlation of the basic physiology with clinical hypertension.

With a chapter on the circulation in hypertension, Doctor Pickering comes to the conclusion that "arterial pressure is regulated in very much the same way, *with a not grossly dissimilar precision*, in those with high and those with lower pressures." This naturally leads to his concept that essential hypertension is not due to a qualitative difference but merely a quantitative difference. He presents in detail his method of arriving at this conclusion, his investigations of variation in blood pressure, genetic factors and environmental factors and the influences of these on the "quantitative difference." This section of the book is the real reason for the book and should, therefore, be critically reviewed.

A detailed analysis of this section cannot be presented but, since the author arrives at his conclusion by a statistical analysis of the blood pressure of 2,031 people, several questions arise. In addition to the usual question of the validity of the population sample and the assumption that these people have no disease which might effect blood pressure, one would question the fact that the author arbitrarily flattens his curves in the older age groups because he says "it seems unreasonable to suppose that the rate of rise should continue to steepen indefinitely." The curve should fit the data or, if there is insufficient data, this portion of the curve should be deleted. The author is in the parodoxic situation of

ecrying the use of a dividing line between normal nd abnormal but is still using literature based on a "arbitrary normal" to support his theses. Some udies are based on systolic pressure only and may ave no relation to diastolic hypertension. The emainder of the book, aside from chapters on prog-osis and treatment of hypertension, consists of everal chapters on diseases which lead to secondary ypertension. These chapters are good reviews of hese diseases. There is an excellent chapter on yelonephritis. The author properly stresses the im-ortance of this disease. There are also four tables or the calculation of the age and sex-adjusted core, according to Pickering's method.

Although one may not agree with the conclusions rawn from the evidence presented, the book is most eartily recommended to the thoughtful reader. One cannot read this book without carefully exam-ining one's own concepts of high blood pressure because they are all analyzed critically by the au-thor. One cannot help but admire the thoroughness with which Doctor Pickering has considered each detail. The book serves a good purpose. It is not for the casual reader of summaries.

JEROME M. WALDRON

Electrocardiographic Test Book. *Editor, Travis Winsor*, fabrikoid, $5.00, Two Volumes. Volume I, 167 pages, Volume 2, 132 pages, illustrations throughout. New York, American Heart Asso-ciation, Inc. 1956.

The 2-volume "Electrocardiographic Test Book" recently published by the American Heart Associa-tion cannot fail to make the teaching of clinical electrocardiography more stimulating, entertaining, and enriching. The first volume contains a series of 119 electrocardiograms, each of them well repro-duced. They include the problems encountered in the usual heart station and internist's office. Each set of tracings is accompanied by multiple-choice questions. For each page of Volume 1 a correspond-ingly numbered page of Volume 2 provides the correct answer and a lucid explanation. A brief case summary is given, often with additional visual aids such as roentgenogram of the chest, additional electrocardiograms, phonocardiogram, or kymo-gram.

The second section of the Test Book groups 237 multiple-choice questions into categories such as "arrhythmias," "intrinsicoid deflection," "leads," "theory," and many others. Similarly numbered pages of the companion volume again provide the answers, often with a brief explanation. Finally, in an appendix, there have been provided tables that summarize most of the mensuration data available at this time. A complete index to the electrocardio-graphic reproductions is provided.

The Advisory and Review Panel under the direc-tion of Dr. Winsor is to be commended. The general plan has been well conceived and clearly executed, and a wealth of material has been included. The records are excellent examples of the conditions they represent. Artifacts have wisely been included as representing the type of problems physicians must cope with.

The neophyte will have much to gain from study of these test books. More advanced cardiologists will appreciate the manner in which more sophisticated concepts such as peri-infarction block, Cabrera's systolic and diastolic overload, and the significance of the U wave have been included.

It might have been stimulating to have included some introduction to "vector thinking" in certain of the explanations. These 2 volumes certainly belong in the library wherever electrocardiography is being taught or electrocardiograms are being read.

JERROLD S. LIEBERMAN

Thrombosis and Embolism. Proceedings of the First International Conference, Basle, 1954. *Edited by Th. Koller and W. R. Merz.* Basle, Benno Schwabe and Company, 1955, 1316 pages. $17.75.

This volume represents a condensed survey of the many disciplines contributing to the increased understanding of vascular thrombosis. In abbrevi-ated form in one volume it includes historical reviews, panel discussions, descriptions of new technical procedures, and original investigations and clinical studies of various aspects of thromboembolic disease including the heart and brain. Many abstracts are concerned with the evaluation of various medical and surgical forms of therapy. The majority of the contributions are by European investigators. Sum-maries of all articles, however, are provided in English as well as in German and French. This compilation provides an excellent résumé of past and present thinking in the broad area of medicine involving thromboembolic phenomena.

STANFORD WESSLER

Principles of Renal Physiology. *Homer W. Smith.* New York: Oxford University Press, 1956, 237 pages, 24 figures, 5 plates. $5.00.

This is a wonderfully compact and detailed summary of current knowledge of the principles and minutiae of renal function. Though based largely on clearance technics in mammals and in man as perfected and used in his laboratory and elsewhere, the author draws freely on his extensive knowledge of comparative physiology, anatomy, and of organic evolution pointing out, all the while, that no other species can serve as a model for man. Neither are newer tools of investigation such as electron micros-copy and tissue culture methods omitted. Areas of incomplete information on subjects such as the comparative importance of glomerular filtration and tubular reabsorption in proteinuria, the particular electrolyte and other effects whereby diuresis is

produced by organic mercurials, and the chloruretic and natriuretic actions of antidiuretic hormone are pointed out.

The liberal use of footnotes and appendices and reliance upon a highly selected bibliography greatly simplify the flow of history, facts, and ideas in the body of the text. On the other hand the lack of detailed references may be felt in using this volume, even though the detailed bibliography of *The Kidney: Structure and Function in Health and Disease* by the same author is available to the reader. An interesting feature of the text is the inclusion of intellectually stimulating problems that test the reader's comprehension and dexterity in areas just discussed by the author. Question 15 differs in asking for suggestions on the text as a whole. The reviewer wishes to suggest that in subsequent editions the terms acids and bases be replaced by phrases that lend themselves more readily to the incorporation of the proton concept, perhaps by anions and cations, and that there be included an exposition of titratable acidity.

This monograph will be a *vade mecum* for all serious students of renal physiology.

T. S. Danowski

Malformaciones y Tumores Vasculares Congenitos de los Miembros. *F. Martorell and B. Salleras.* Barcelona, Spain, Publicaciones Medicas Jose Janes, 1955, 143 pages, 59 illustrations.

The subject of this book is established in its title: "Congenital Malformations and Vascular Tumors of the Extremities."

In the first chapter, the authors discuss the differences between vascular malformations that develop as a consequence of hydrodynamic anomalies (angiectasias) and those that resemble the other tumors in their autonomous growth (angioblastomas). Within these 2 groups the congenital vascular malformations are classified in a very intelligible manner, so that the sometimes confusing nomenclature on the subject is clarified.

Chapters II, III, IV, and V are concerned entirely with the Klippel Trenaunay (Parkes-Weber) syndrome. First the authors describe the different theories concerning its pathogenesis, discussing them rather extensively. A series of 24 case histories of Klippel-Trenaunay syndrome is then presented. Most of the patients in the series were treated surgically. An analysis of the symptomatology follows the case histories. Finally, in the chapter concerning treatment, the pathogenesis of this syndrome is again discussed.

The following chapters are devoted to varicose veins due to arteriovenous fistula, cirsoid aneurysms, arterial and venous acinous hemangiomas, muscular hemangiomas, brachial (osteolytic) hemangiomatosis, lymphangioma, and congenital lymphedema.

The organization of the material is good, with presentation of illustrative cases in most of the chapters, and the literature on the subject is widely quoted. The greater portion of the rather limited space of the book is dedicated to the Klippel-Trenaunay syndrome (4 chapters out of 12 and 76 pages out of 143); thus the authors fail to discuss in greater detail other vascular anomalies of more, or at least, equal importance.

The book is nicely printed and some of the illustrations are of excellent quality.

Enrique Urdaneta

Le foie et la veine porte. *G. Albot, R. André, . . Caroli, R. Cattan, M. Champeau, A. Charbonnier, C. Couinaud, Decoularé R. Dupuy, J. Etévé, F. Fauvert, C. M. Fayé, A.-L. Froehlich, J. Herman, Cl. Houdard, E. Housset, L. Leger, A. Lemaire, J. Lunel, Ch. Nezelof, F. Poilleux.* Paris, Masson et Cie, 1955, 382 pages, 98 figures, 4 plates in color. 3.200 fr.

This volume contains presentations and discussions of the monthly meetings of the French National Academy of Gastroenterology held at L'Hotel Dieu during 1954. Many interesting problems such as the role of the liver and biliary tract in hemolytic icterus, infectious hepatitis, intrahepatic cholostasis, and cholangiolotic and cholostatic cirrhosis are discussed. The pathology of the portal circulation is analyzed from a variety of points of view. Pertinent case histories are presented in most of the chapters.

Of particular interest to this reviewer are the conferences on exploration of the portal system. Here the hemodynamics and biologic characteristics of the circulation are analyzed and a very valuable discussion on the use of splenoportography in the diagnosis of liver cirrhosis and portal hypertension is presented.

Liver biopsy and liver function tests are evaluated from a practical viewpoint for the clinician. Surgical procedures are also discussed to some extent.

It should be noted that although different aspects of the argument are presented, the bibliography is rather inadequate. There are also a number of minor errors of proof reading and some of the figures have apparently incorrect labels. There are excellent color plates as well as illustrations in black and white. The book should be of great interest and can be recommended to the clinician and investigator as a source for stimulating reference.

Enrique Urdaneta

ABSTRACTS

BLOOD COAGULATION

Beamish, R. E., and Storrie, V. M.: Severe Haemolytic Reaction Following the Intravenous Administration of Emulsified Vitamin K_1 (Mephyton). Canad. M. A. J. **74:** 149 (Jan.), 1956.

Mephyton is not as free of toxicity as has been thought. A severe hemolytic reaction following its intravenous administration has been observed. There is evidence that Mephyton is usually as effective orally as it is intravenously, and it is suggested that the use of the oral route may avoid an occasional toxic reaction of the type here described.

BERNSTEIN

CONGENITAL ANOMALIES

Navratil, L., Wenger, R., and Kaindl, T.: On the Etiology of Congenital Heart Disease. Arch. Kreislaufforsch. **22:** 225, 1955. Abstracted, Circulation **14:** 1116 (Dec.), 1956.

Shephard, R. J.: The Influence of Age on the Hemoglobin Level in Congenital Heart Disease. Brit. Heart J. **18:** 49 (Jan.), 1956.

The hemoglobin content of the blood was determined in 350 unselected individuals with congenital heart disease, 166 acyanotic and 184 cyanotic. These ages ranged from 2 to 60 years. Like the normal, the hemoglobin level rises until adulthood but the curve is set at a level lower than normal in the acyanotic and higher in the cyanotic group. For this reason, up to age 20, 85 per cent of the cyanotic group can be recognized solely by the hemoglobin level. Beyond this age, the 2 hemoglobin curves merge, perhaps because the more severely cyanotic subjects have died.

SOLOFF

Hara, M., and Johnson, N.: An Anatomically Atypical Patent Ductus Arteriosus. Ann. Surg. **143:** 136 (Jan.), 1956.

The authors described a case of an anatomically atypical patent ductus arteriosus in a boy, 7 years of age. At operation a broad-window type of patent ductus arteriosus was found, entering the transverse arch of the aorta proximal to the left subclavian artery. This was unassociated with any other gross congenital cardiac or aortic abnormality.

The proximal portion of the main pulmonary trunk was greatly enlarged and dwarfed the juxtaposed aorta. The fistula measured 1.3 cm. in width. With curved ductus clamps of the Potts type, the communication was divided and the rents in the wall of the aorta and pulmonary artery were closed with continuous sutures. The patient's postoperative course was uneventful, except for a sinus tachycardia that subsided after digitalization.

ABRAMSON

Legrand, R., Vandecasteele, J., Desruelles, J., and Breynaert, R.: Isthmic Stenosis of the Aorta: Operation of Crafoord-Gross and Reestablishment of Vascular Continuity by means of a Graft Preserved in Formaldehyde. Arch. mal. coeur **49:** 67 (Jan.), 1956.

In this case the length of the stenosis was 6 cm., and the elasticity of the aorta was poor, so that it could not be mobilized sufficiently for an end-to-end anastomosis. The patient is in perfect health 10 months after the operation and has a normal pulse pressure in the legs.

LEPESCHKIN

Lang, H. T., and Nadas, A. S.: Coarctation of the Aorta with Congestive Heart Failure in Infancy—Medical Treatment. Pediat. **17:** 45 (Jan.), 1956.

The question of the optimum age in which to correct surgically coarctation of the aorta is discussed by the authors. Some infants within the first year of life have been subjected to operation because cardiac failure had developed. The results of surgery in these patients are not good. The authors present the findings in 9 infants who had uncomplicated coarctation clinically and who, in the first year of life, presented signs of congestive heart failure. These infants were treated by medical means with digitalis, diuretics, chemotherapy for intercurrent infection, and a sodium-free formula. The cardiac failure was well controlled and the infants survived and have developed fairly well with the slowness natural in any infant with coarctation. The authors believe that such infants with coarctation can be treated medically and surgery can be delayed until later in life when survival rate is much more favorable.

HARVEY

Arvidsson, H., Karnell, J., and Moller, T.: Multiple Stenosis of the Pulmonary Arteries Associated with Pulmonary Hypertension Diagnosed by Selective Angiocardiography. Acta. radiol. **44:** 209 (Sept.), 1955.

The diagnosis of stenosis of the main or smaller branches of the pulmonary artery as a cause of pulmonary hypertension was demonstrated in 4 patients by the use of selective angiocardiography. Poststenotic dilatation was almost invariably present. One of these 4 patients had an atrial septal defect in addition to the multiple peripheral pulmonary arterial stenosis. Three of the 4 had associated systolic murmurs, 2 with maximal intensity over the pulmonic area; 1 had a continuous murmur simulating patent ductus arteriosus. The cause of the stenosis was believed to be due to aplasia of the vascular supply of the lung. Often the circulation was supplied by marked arteries. Although rare, it is an additional cause of pulmonary hypertension.

SCHWEDEL

Heath, D., and Whitaker, W.: The Pulmonary Vessels in Patent Ductus Arteriosus. J. Path. & Bact. **70:** 285 (Oct.), 1955.

A histologic study was made of lung biopsies done at operation for closure of patent ductus arteriosus in 12 individuals varying in age from 6 years to 58 years of age. Pulmonary vein pressures were measured at catheterization prior to operation in 9 individuals. Five individuals had normal pressures, 2 moderately elevated, and 2 severely elevated (70 mm. Hg mean pressure). The patients with normal pulmonary pressures showed histologically perfectly normal pulmonary arteries, arterioles, and veins. The patients with severe pulmonary hypertension had medial necrosis and atheroma in elastic arteries, medial hypertrophy and occlusion of lumen of the muscular pulmonary arteries, and in the arterioles there was hypertrophy of the media and intimal proliferation. The authors believe that media in the pulmonary arterioles is a congenital abnormality, which is not solely responsible for the increased vascular resistance. Changes in the intima and lumina of the vessels are irreversible and lead to persistent pulmonary hypertension.

HARVEY

Brewer, D. B.: Fibrous Occlusion and Anastomoses of the Pulmonary Vessels in a Case of Pulmonary Hypertension Associated with Patent Ductus Arteriosus. J. Path. & Bact. **70:** 299 (Oct.), 1955.

An excellent histologic study of the blood vessels in the lung of an individual with a patent ductus arteriosus, pulmonary hypertension, and reversal of flow is presented. The author has reconstructed graphically the arterioles by plotting graph diagrams of serial sections (10 micron separation) of several blocks of tissues.

The arterioles show occlusion of the lumina in many areas by fibrous tissue. Immediately before the occlusion there arise thin walled vessels clearly demonstrated to be arterial anastomotic channels. Heretofore, these thin walled vessels have been thought to be abnormal arteriovenous anastomoses of congenital origin. The same type of study was done in blocks of tissue from the lungs of a patient with pulmonary bilharziasis and the histological findings were identical.

HARVEY

CORONARY ARTERY DISEASE

Fagin, I. D., and Guidot, J. M.: Problems in the Treatment of the Diabetic Cardiac Patient. Geriatrics **4:** 49 (Jan.), 1956.

One hundred and seventy-four patients with diabetes and heart disease are reviewed with emphasis on the problems that may arise in diabetic patients with angina, myocardial infarction, and congestive failure. In most of the patients, the coexistence of the 2 diseases did not complicate the treatment of either. In a small group of patients (13 per cent), including 10 with myocardial infarction and 5 with congestive failure, the breakdown of diabetic control was severe and posed major therapeutic problems. None of the 40 deaths in the series was attributable to diabetic coma or complicating electrolyte imbalance.

RINZLER

Kattus, A. A., Jr., Watanabe, R., Semenson, C., Drell, W., and Agress, C.: Serum Aminopherase (Transaminase) in Diagnosis of Acute Myocardial Infarction. J. A. M. A. **160:** 16 (Jan. 7), 1956.

Serum aminopherase levels on 68 blood samples from 11 normal subjects and 22 patients not suspected of having acute myocardial damage or liver disease averaged 20.5 units with a range of 11 to

42 units. Elevation of levels occurred in 13 of 14 patients with proved myocardial infarction. One patient who died 3½ hours after onset of infarction had a normal serum aminopherase. Usually after myocardial infarction the serum aminopherase level begins to rise after a delay of 6 to 12 hours with a peak in 24 to 36 hours. There is a decline to normal by the fifth or sixth day. Patients with coronary insufficiency (even with marked ST-T electrocardiographic changes) did not have elevations of serum aminopherase levels. Patients with liver disease have serum aminopherase level elevations but there is a prolonged time-concentration curve in liver disease.

KITCHELL

Vogelpoel, L., and Schrire, V.: Myocardial Infarction. Its Racial Incidence in Cape Town. Lancet **2:** 1108 (Nov.), 1955.

An electrocardiographic study was made at the Groote Schuur Hospital in Cape Town where the very large clientele is divided among Europeans, "Cape Coloured," and Bantu in the ratio of 2:2:1, respectively. In 1953 and 1954, 5,004 electrocardiograms were taken on adults in response to routine clinical request. Of these, 550 showed evidence of myocardial infarction. Furthermore, of the "infarct records," 448 were from Europeans, 100 from "Coloured," and only 2 from Bantu. More electrocardiograms were taken in Europeans than in nonEuropeans. However, 13.54 per cent of European electrocardiograms showed infarction, whereas the corresponding figures were 6.8 and 0.9 for "Coloured" and Bantu.

MCKUSICK

Bronte-Stewart, B., Keys, A., and Brock, J. F.: Serum-Cholesterol, Diet, and Coronary Heart Disease. An Inter-Racial Survey in the Cape Peninsula. Lancet **2:** 1103 (Nov.), 1955.

This study is a continuation of others by Keys and co-workers who in several different populations have demonstrated a relationship between the death rate from coronary heart disease, the mean serum cholesterol level and the proportion of calories derived from total dietary fat. In South Africa, there are 3 groups—Europeans, "Cape Coloured," and Bantu—each of which adheres to its traditional customs, particularly as regards diet. The authors quote a diet survey that concluded that fat constituted 35 per cent, 25 per cent, and 17 per cent, respectively, of the total calories of the diet of these 3 groups. Study of total serum cholesterol and of cholesterol in the β-lipoprotein fraction of serum revealed a parallel series of values. Statistics were quoted which indicate that death ascribed to coronary artery disease is about twice as frequent among the Europeans as among the "Cape Coloured" whereas in the Bantu it is "exceedingly rare."

MCKUSICK

Applebaum, I. L., Bernstein, A., Levine, B., Shoshkes, M., Becker, M., Carrol, W., Goldberg, H., Kaufman, J., Kuperman, H., Lewis, S., Nudelman, W., Perelman, A., Rowen, M., Shulman, P., Simon, F., Weiss, F., Weiss, W., and Zucker, I.: Myocardial Infarction: A Clinical Review of 888 Consecutive Cases. J. Newark Beth Israel Hosp. **6:** 305, 1955.

The authors reviewed 888 consecutive cases of myocardial infarction admitted to the Beth Israel Hospital from 1947 through 1953. The effect of diabetes, hypertension, family history, occupation, etc. on the etiology of myocardial infarction was studied. Symptomatology, physical signs, and laboratory data are reviewed in relation to the infarction. The value of Dicumarol was carefully studied and it was found that the results with the anticoagulants were no better than without them. The significance of this finding is discussed. The deaths in this series were carefully reviewed and the autopsy findings studied and reported. The authors carefully compared their results with those of previous studies and point out the points of similarity and divergence with possible explanations for the differences.

BERNSTEIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND PHONOCARDIOGRAPHY

Eliakim, M., and Braun, K.: Observations on the Relations of Electrical and Mechanical Events in Cardiac Arrythmias. Am. Heart J. **51:** 61 (Jan.), 1956.

The latent period between the onset of the electric and mechanical systole, the length of the electric and mechanical systoles, and the height of the systolic and diastolic pressures were measured by simultaneous recording of right ventricular pressure and electrocardiogram in 22 patients suffering from congenital or acquired heart disease and compared in normal and abnormal beats. Ectopic beats appearing in the ejection phase caused a broadening of the mechanical systole of the antecedent beat and maintained its diastolic pressure at a level higher than normal. Ectopic beats appearing in the isometric ventricular relaxation phase usually had a high initial pressure, prolonged electric-mechanical latent period, decreased systolic pressure, and shortened mechanical systole. Ectopic beats appearing in the rapid ventricular filling phase had a normal or elevated initial pressure, normal or prolonged electric-mechanical latent period, normal or decreased systolic pressure and, frequently, shortened mechanical systole. Ectopic beats appearing in the diastase of the antecedent beat had a normal initial pressure, usually a normal electric-mechanical latent period and systolic pressure, and a short, normal, or prolonged mechanical systole. Successive ectopic beats produced a lowering of systolic

pressure and a rise in diastolic pressure in the ventricle, thus interfering with heart performance.

RINZLER

Aixala, R., Muniz Sotolongo, J. C., Sanchez, G. A., Fojo Echevarria, P., Gomez Hernandez, A., Triay, R., and Sanchez, R.: Experimental Production of the Wolff-Parkinson-White Syndrome Through Direct Current Stimulation of the Epicardial Surface. Rev. cubana de cardiol. **16:** 441, (Sept.), 1955.

Single complexes of the Wolff-Parkinson-White configuration could be obtained by direct mechanical stimulation of the ventricular surface. They also appeared during application of direct currents (75 volts, 0.25–1 milliamperes) to the surface of the right ventricle and septum, but not to the left ventricle. Isolated ventricular extrasystoles occurred in both cases.

LEPESCHKIN

Furbetta, D., Bufalari, A., and Santucci, F.: Chronological Relations between the U Wave of the Electrocardiogram and Mechanical Intervals of the Cardiac Cycle. Folia cardiol. **14:** 457, 1955.

In 30 normal persons the end of systolic ejection (first large vibrations of the second heart sound) appeared on the average 0.02 sec. after the end of T (0.04 before to 0.05 after), at the beginning of U and 0.08 sec. (0.04 to 0.13 sec.) before the apex of U. In 100 patients with heart disease it appeared up to 0.10 sec. before or after the end of T, but its relation to the beginning of U was much more constant (0.06 sec. before to 0.02 after, with an average of 0.015 before). It appeared 0.03 to 0.16 (on the average 0.09) sec. before the apex of U. The greatest delay of U with respect to the end of systole was observed in heart disease involving the left ventricle. In 6 cases of mitral stenosis this delay decreased after commissurotomy. In cases showing a split second sound the beginning of U coincided with the first, aortic component. U coincided with the period of rapid filling in the esophageal rheocardiogram and with the protodiastolic negativity of intraventricular pressure curves. The third heart sound appeared 0.01 to 0.12 (on the average 0.05) sec. after the apex of U and about 0.05 sec. before the end of U. In hypocalcemia U is often superimposed on T but its extrapolated beginning coincides with the second heart sound as in normals. When Q-T is shortened, the T-U interval is always prolonged and U begins with the second heart sound. In extrasystoles the second heart sound and the U wave both appear earlier with respect to the T wave, causing superposition of U on T.

LEPESCHKIN

Furbetta, D., Santucci, F., and Bufalari, A.: Clinical Significance of Negative U Waves. Folia cardiol. **14:** 477, 1955.

Negative U waves in one or more routine leads (except III, aV_R and aV_L) were found in 2.3 per cent of 4,500 consecutive electrocardiograms. In these 200 cases variations in the duration of the T-U segment were much greater than in normal subjects, and the average values were greater. In cases with hypertension (63 per cent of the 200 cases) the negative U waves tended to appear in leads I, aV_L and V_5-V_6, corresponding to marked clockwise deviation of the U-wave axis in the frontal and horizontal planes (seen from the front and above). The amplitude of the negative as well as positive U wave was greater in hypertension associated with other cardiac abnormalities such as angina (17 per cent) than in pure hypertension. The clockwise displacement of U axis in the frontal plane tends to increase as the systolic pressure rises to 200, but does not increase any further with further increase of pressure. The maximal voltage of the negative U wave shows no relation to pressure. The U-wave vector tends to become more perpendicular to the frontal plane as the pressure rises, while the incidence of negative U waves in precordial leads falls and that in limb leads rises. In cases showing marked clockwise rotation of the U-wave axis the aorta was markedly enlarged, while in those showing counterclockwise deviation the heart was usually not enlarged; normal hearts were found in 51 per cent of the hypertensives. In cases with angina (12 per cent) with large hearts the U-wave axis was more deviated and U-wave voltage smaller than in those with not enlarged hearts. In mitral stenosis (2 per cent), the negative U waves appear in leads III, aV_F and V_1, corresponding to counterclockwise rotation of the U-wave axis in the frontal and horizontal planes. In cases with involvement of both ventricles U may become negative in all precordial leads. In the great majority of cases, the negative U wave tends to be opposed to the main direction of QRS, while it tends to be of the same direction as the T wave in less than half of the cases. In 25 of the 200 cases inverted U waves were the only abnormal electrocardiographic finding; all these persons were between 27 and 60 years of age, 13 had hypertension, 8 angina pectoris, 3 mitral and aortic valvular disease, and 1 "chronic myocardial disease." In all these cases the negative U waves appeared in left precordial leads. In 1 case the heart was accelerated, U became positive, and T less pointed after inhalation of amyl nitrite. In 1 apprehensive patient with hypertension, the negative U wave became less negative without change of heart rate when the patient calmed down. In 1 case of aortic coarctation, negative U waves in lead I became positive with disappearance of hypertension after operation. In 1 case of hypertension with angina pectoris, U became deeply negative in V_5-V_6 after exercise.

LEPESCHKIN

Calderón Montero, J., and Salces Blesa, A.: The Electrocardiogram in Cardiac Tamponade. Experimental Studies. Rev. españ. cardiol. **9:** 192, 1955.

In 17 dogs the carotid artery was connected with the pericardial cavity by means of a tube. The arterial blood pressure fell immediately to almost zero, while the venous and intrapericardial pressures rose gradually. The QRS axis showed immediate deviation to the left, which is attributed to upward displacement of the cardiac apex by the intrapericardial blood. One and one half to 2 minutes later the electrocardiogram voltage started to decrease; because of its late appearance, this decrease is attributed not only to short-circuiting effects of the intrapericardial blood, but also to decrease in the membrane potentials due to anoxia. Later the voltage may increase again (in the published curves this was always accompanied by widening of QRS). S-T in leads II–III showed depression in all cases, while elevation was said to appear only once; however, the published curves often show transient elevation of the S-T junction, especially in comparison with a depressed P-R segment. The atrial rhythm showed a progressive slowing, often accompanied by changes in the configuration of P; usually a ventricular ectopic rhythm took over, but sometimes this rhythm originated in the A-V node. This period was usually followed by a return of sinus rhythm and later by A-V conduction disturbances. Ventricular fibrillation appeared in all cases, but in some of these it disappeared later and ventricular standstill with slow atrial rhythm occurred. The higher incidence of fibrillation in pericardial tamponade than in exsanguination is attributed to the sudden fall in arterial blood pressure in the former.

LEPESCHKIN

Facci, M., and Lubich, T.: Electrical Systole. Variations of Q-T in Relation to Age, Sex, Pregnancy, Postural Changes, Respiration, Exercise and Ocular Pressure in Normal Subjects. Folia cardiol. **14:** 265, 1955.

The Q-T interval, corrected for the heart rate according to the square root formula, was 0.34 in children 2 to 6 years of age. In adults no difference in Q-Tc was found between the sexes. After standing up, Q-Tc increased whenever the rate increased, but in 1 case it showed no change in spite of tachycardia. The increase was usually smaller after previous medication with ergotamine, and is therefore dependent on sympathetic stimulation. After lying down, Q-Tc returned to its initial value without overshooting. Normal inspiration caused increase of Q-Tc related to the tachycardia in 60 per cent, and no change in 40 per cent. During forced expiration (Valsalva), Q-Tc increased in all cases showing tachycardia, decreased in all cases showing bradycardia but also in some not showing any change in the heart rate. After the Master exercise test, most cases showed increase of Q-Tc, a few showed no change, and one showed normalization of a previously increased Q-Tc with no change in rate; this latter reaction is considered a sign of good training. Ocular pressure caused shortening of Q-Tc in all subjects.

LEPESCHKIN

Furbetta, D., Bufalari, A., and Santucci, F.: Definition and Normal Electrocardiographic Limits of the U Wave. Folio cardiol. **14:** 339, 1955.

In 100 normal persons at rest, no significant difference in the U waves was found in tracings taken with different amplifier electrocardiographs. The initial branch of the U wave was always shorter than the terminal branch, in leads where U was positive as well as in those where it is negative. The U wave was found in 99 per cent in lead V_3 and 92 per cent in lead II, but only 58 per cent in V_6 and 54 per cent in aV_L. In V_2, 29 per cent had a U wave of 1 or more mm., while in V_3 this percentage was 23, with 2 cases showing a U wave of 2 mm. In lead III, 2 cases had U of 1 mm., while in aV_L U was negative in 19 cases. U was negative in no other leads except aV_R. The duration of the U wave ranged between 0.15 and 0.22 sec. and decreased with increasing heart rate. The T-U interval (measured between the end of T and beginning of U) showed little dependence on the heart rate, but tended to be negative (superposition of U on T) at very high rates in children. The U wave was usually highest in V_2, while the transition zone of QRS was usually situated in V_3. In cases with the transition zone displaced to the right, the U-wave maximum usually coincided with this zone or was to the left of it, while if the zone was displaced to the left, the U wave maximum was usually to the right of it. As the zone moved from right to left from V_1 to V_5, the location of the U-wave maximum also moved from V_1 to V_4, while its voltage at first increased, then decreased. In cases with left axis deviation of QRS the transition zone was usually situated in left precordial leads while the U-wave maximum was situated in right precordial leads, while in cases with normal or right axis deviation both the transition zone and the U-wave maximum were usually in midprecordial leads.

In leads V_1–V_2 U usually exceeded 10 per cent of T, and was positive even when T was negative; in V_3–V_4 U usually was about 10 per cent of T, while in V_5–V_6 U was usually less than 10 per cent of T. The quotient T/U ranged from 2 to 50, with an average of 10.6, but the scatter was very great. The cases with tall T waves had high quotients while those with tall U waves had low quotients. This lack of definite correlation between T and U is interpreted as not favoring a causal relation between these waves.

Tall and slender young persons tend to have high voltage of all waves, including U, in precordial leads; on the other hand, in pregnancy all waves tend to be low. In men, the highest voltage of U in all leads

was on the average 0.71 mm., while in women it was 0.38 mm. In men there is a marked increase in the average highest U-wave voltage with age until the third decennium, and a gradual decrease from then on; in women there is no change with age except that the first and last decenniums have lower values. In the first and second decennium U is lower compared to the T wave than in the fourth through the eighth decenniums. The blood pressure and heart rate do not seem to affect the U wave amplitude noticeably. In deep inspiration U tends to become taller and of shorter duration. After the Master exercise test U usually becomes taller in the precordial leads V_1–V_4, but never exceeds 150 per cent of its resting value. Sometimes the elevation is only an apparent one, due to better separation of T and U. The T/U quotient always decreases up to 50 per cent.

LEPESCHKIN

Foscarini, M., Facchini, G., and Bortolotti, G. C.: On Coronary Sinus Rhythm. Folia cardiol. **14:** 431, 1955.

Coronary sinus rhythm was observed in 16 of 15,000 electrocardiograms (1.1 per cent); 3 of these had hypertensive, 6 coronary, and 2 rheumatic heart disease; 1 had pericarditis and 4 had apparently normal hearts, with 3 of these showing symptoms of neurocirculatory asthenia. The P wave was always negative in II–III and aV_F, usually positive in aV_R, always positive or isoelectric in aV_L and I, and often negative in V_4–V_6. In 1 case with cardiac catheterization P was positive in the upper and lower atrial region and completely negative in a mid-atrial position. The average rate of the rhythm was about 65 per min., and when transitions between it and sinus rhythm were observed, the latter always had the higher rate. P-R measured 0.10–0.18 sec., and in all cases except one, transition to sinus rhythm was accompanied by increase of P-R. The case in which P-R was 0.18 showed a P-R of 0.23 with sinus rhythm. The Valsalva maneuver caused the rhythm to appear in 4 cases, to disappear in 1 case, and did not influence it in 2 cases.

LEPESCHKIN

Kunos, I., and Garán, V.: Ballistocardiographic Studies in Valvular Heart Disease. Ztschr. Kreislaufforsch. **44:** 814, 1955.

Registration of the electromagnetic ballistocardiogram synchronously with the right intraventricular pressure curve shows that the H wave corresponds to the isometric phase of contraction while the I-J branch corresponds to rapid ejection and the beginning of the pulmonary pressure curve. In cases of mitral stenosis with pulmonary hypertension and in those cases of aortic regurgitation, an extra wave often appears in the H-J branch; this extra wave is attributed to opening of the semilunar valves. A vibration in the K wave is attributed to opening of the A-V valves. In aortic regurgitation, a typical finding is increased amplitude of J and K, and this is present also when there is additional mitral stenosis. A similar finding was present in persistent ductus, disappearing after the operation.

LEPESCHKIN

Blume, J.: Summary of the Results of Mathematical Analysis of Phonocardiograms in Children. Ztschr. Kreislaufforsch. **44:** 820, 1955.

In 27 normal children 10 to 13 years old, moderate exercise caused an increase in the range of frequencies contained in the first heart sound, in the upper limit of these frequencies and in the sum of the initial amplitudes of these frequencies. These changes disappeared after 20 minutes and were not present in the second heart sound. In 21 children with presumptive cardiac abnormalities, these changes usually were greater and did not disappear completely after 20 minutes; in several of these cases the frequency range and the sum of initial amplitudes decreased.

LEPESCHKIN

Rence, W. G., Cullen, S. C., and Hamilton, W. K.: Observations on the heart sounds during anesthesia with cyclopropane or ether. Anesthesiology **17:** 26 (Jan.), 1956.

Objective recordings of the heart sounds at the cardiac apex made in 15 patients subjected to various levels of cyclopropane or ether anesthesia revealed changes correlated with the depth of anesthesia.

With patients awake or in light anesthesia, the first heart sound was of higher intensity than the second, producing the familiar normal lub-dup. As the dosage of the anesthetic was increased, the second heart sound became more prominent and developed a sharp, slapping or metallic character. With further deepening of anesthesia or with excessive dosage, the first and second sounds became equal in pitch and their intensity was reduced to the point of muffling. The authors believe that the concentration of anesthetic to which the heart is exposed is the critical factor in the production of the changes noted. The changes in heart sounds produced by a certain dose of anesthetic often preceded the clinical signs of the depth of anesthesia.

SAGALL

Esch. I., and Heeger, H.: Closure of the Tricuspid Valve in the Venous Pulse in A-V Block. Ztschr. Kreislaufforsch. **45:** 29 (Jan.), 1956.

In some cases of A-V block a small sharp wave appears immediately after the a wave venous pulse; about 0.20–0.24 sec. after the beginning of P in the electrocardiogram and at the apex of the T_P wave. This wave is attributed to closure of the tricuspid valve.

LEPESCHKIN

Sapin, S. O., Donoso, E., Braunwald, E., and Grishman, A.: Spatial Vectorcardiography in the Di-g-

nosis of Congenital Cardiac Malformations. Pediatrics **17:** 93 (Jan.), 1956.

The theory of vectorcardiography is presented as well as practical means to record vectorcardiograms. Examples of vectorcardiograms done on infants with congenital heart disease are presented, as well as comparisons of these results with the conventional electrocardiogram. The authors feel that right ventricular hypertrophy is better demonstrated by the vectorcardiogram than by axis deviation on the conventional cardiogram, and they advocate the use of the vectorcardiogram in the diagnosis of congenital heart disease.

HARVEY

Castellanos, A., Jr., Azan Cano, L., Calvino, J. M., and Taquechel, N.: Action of Ectopic Foci on the Automatic Centers of the Heart. Rev. cubana cardiol. **16:** 419 (Sept.), 1955.

In the frog, electrically induced extrasystoles are usually followed by a longer post-extrasystolic pause than would correspond to the interval between automatic beats previously present in the stimulated region. This effect is more pronounced in the ventricle than in the A-V region or venous sinus; it is especially common in early extrasystoles and after repeated stimulation, but in old anoxic preparations it occurs independently of the position of the extrasystole in the cycle. Retrograde conduction either does not exist or does not have this effect. In 2 clinical cases atrial extrasystoles caused temporary slowing of the sinus rhythm, followed by escape beats from the coronary sinus or the ventricle. In 1 case such depression was caused by ventricular extrasystoles with retrograde conduction. In 1 case of A-V nodal tachycardia, several conducted sinus beats caused temporary suppression of the ectopic center. However, in another case this tachycardia was regularly elicited by ventricular extrasystoles, which accordingly had a facilitating effect on the ectopic rhythm. In idioventricular rhythm ventricular extrasystoles usually are followed by depression and sometimes by a complete temporary suppression of this rhythm.

LEPESCHKIN

Bjerke, G., and Ström, G.: Attacks of Ventricular Fibrillation with Subsequent Massive T-Wave Inversion in a Case of Complete A-V Block. Acta med. scandin. **152:** 479 (July), 1955.

The case of a woman aged 77 years who was receiving radiologic treatment for gingival carcinoma of the mandible is reported. The patient had known complete heart block. She was given quinidine sulfate 0.3 Gm. daily and on the third day of such treatment began having Adams-Stokes attacks due to ventricular fibrillation. The quinidine was discontinued and ephedrine in doses of 0.025 Gm. was given 3 times daily. The attacks decreased in frequency but for some time the electrocardiograms showed marked T-wave inversion and prolongation of the R-T interval. The patient was still alive some 9 months after the attack of ventricular fibrillation.

ROSENBAUM

Heyman, F.: Movements of the Arterial Wall Connected with Auricular Systole Seen in Cases of Atrioventricular Heart Block. Acta med. scandinav. **152:** 91, 1955.

Sphygmograms on persons with atrioventricular heart block revealed undulations in constant relation with the P-waves of the electrocardiogram. They were usually formed like double waves and traveled in a centrifugal direction at the same velocity as the pulse. An intra-arterial pressure record from the same segment of the artery did not always show corresponding undulations. The nature of the wave is not clear though it is suggested that it may be actively propagated.

BERNSTEIN

Rodbard, S., Mendelson, C. E., and Elisberg, E. I.: Vibration Analysis of Heart Sounds and Murmurs. Cardiologia **27:** 144 (Fasc. 3), 1955.

In an effort to study the nature of normal and abnormal heart sounds, the authors made use of a vibration analyzer. This instrument, which is described, permits recording of sounds in a manner that depicts their frequency components plotted against time. In this way heart sounds are displayed as a series of successive bursts of sound with definite duration and frequency components. Abnormal sounds (murmurs) were found to be similarly composed. This was in contrast to sounds produced by tuning forks that consisted of single horizontal bars at the rated frequency of the individual fork.

In addition, recordings were made of the sounds produced by fluid flowing through soft-walled collapsible tubes under a constant pressure head. These tubes were surrounded by a chamber that made it possible to vary the external pressure on the tubes. When this external pressure was adjusted to allow the tubes to open alternately and collapse with the fluid flowing through it, a sound was produced that could be recorded by means of the vibration analyzer. At this "critical point," the recording consisted of discrete bursts of sound much like those recorded in heart sounds and murmurs. The authors consider, therefore, the possibility that the heart sounds are produced by rapid repetitive events as reproduced experimentally in collapsible tubes.

PICK

Yuceoglu, Y. Z., and Kisch, B.: Periodic Sino-Auricular Block in an Animal Experiment. Exper. Med. & Surg. **13:** 197, 1955.

In an otherwise normal rabbit with increased body temperature, S-A block developed periodically after intravenous injection of 10 mg. of morphine sulfate. The incidence of sino-atrial block became

less and less frequent in this animal within the next half hour. Increasing the vagus tone always caused the sino-atrial block to reappear. During periods of very strong reflex vagus retardation of the heart beat, the S-A block disappeared. After atropine was administered intravenously, S-A block did not appear and application of the same stimuli as before evoked neither an increase of vagus tone nor S-A block.

BERNSTEIN

Friese, G.: The Esophageal Atrial Cardiogram in Persons with Normal and Abnormal Hearts. Arch. Kreislaufforsch. **22:** 288, 1955.

Esophageal cardiograms, registered at the level of the upper part of the left atrium by means of the "Infraton" condenser microphone, showed the greatest amplitude in the recumbent position. In 57 normal subjects it showed an atrial contraction wave, directed upward, beginning 0.04–0.06 sec. after the beginning of the P wave of the electrocardiogram and having a duration of about 0.13 sec.; this wave is attributed to approach of the atria to the spherical form during contraction. The second upward wave is the ventricular wave, beginning about 0.05 sec. after the Q wave and preceding the first heart sound; this wave usually shows an incisura corresponding to the slow oscillations of the first sound, and is attributed to outward movement of the A-V valves prior to their closure. The third upward wave is the atrial filling wave; its summit appears about 0.05 sec. after the beginning of the second sound. In 15 cases of mitral insufficiency the ventricular wave continued directly into a "mitral reflux wave" with an apex immediately after the second sound and sometimes even before it. This wave was of high amplitude in those cases where the left atrium did not show considerable dilatation. In atrial fibrillation with mitral regurgitation the amplitude increases after long pauses; this is not the case in fibrillation without regurgitation. Mitral insufficiency due to left ventricular dilatation showed similar findings. In 32 cases of predominant mitral stenosis curves of type I are characterized by elevated atrial contraction waves, in type II these waves show no ascending but only a descending branch, while type III shows in addition elevation of the ventricular wave with development of a systolic plateau. Types II and III appear in advanced cases. The descending branch of the atrial filling wave shows a sudden decrease in steepness at the time of the opening snap of the mitral valve, so that this relation can be used to differentiate this snap from a reduplication of the second sound due to asychronism of the semilunar valves. Types I and II with diastolic plateau were also found in beginning failure of the left ventricle; they are attributed to delayed emptying of the left atrium. In cases of chronic cor pulmonale the atrial curve shows the same changes as in those with left ventricular overload.

LEPESCHKIN

ENDOCRINE EFFECTS ON CIRCULATION

Bustamente, R., Perez Stable, E., Casas Rodrigue , R., and De Acosta, O. M.: Myxedema Heart; A Study of 34 Cases. Rev. cubana cardiol. **16:** 40 , (Sept.), 1955.

Symptoms of cardiac insufficiency not attribut - ble to myxedema itself (elevated venous pressu , prolonged circulation time, tachycardia with gall p rhythm) were found in only 6 per cent of the cas . Enlargement of the heart was present in 53 per cen ; in 7 of 9 patients where paracentesis was made pe - cardial effusion was found, but this was usually t o small to account entirely for the heart enlargeme , and was absent in 2 cases with enlarged hearts. Lo v voltage of the T wave is one of the earliest and co - stant signs of myxedema, being absent only in 1 case; the T wave always became normal after trea - ment although it was scarcely modified after pe - cardial tap in 3 cases, and was present also in cas s with normal heart size, so that it cannot be attri - uted entirely to the pericardial effusion. Inversion f T was present in 6 cases; it was present in 2 youn persons with postoperative myxedema of short du - ration, so that it could not have been caused by co - onary sclerosis in thes cases. In 1 case with hyper - tension, a typical left ventricular strain pattern appeared temporarily during treatment. Low volt - age of QRS was present in only 50 per cent, while prolonged P-R or extrasystoles appeared in 3 cases, disappearing after treatment in 2.

LEPESCHKIN

HYPERTENSION

Corcoran, A. C., Dustan, H. P., and Page, I. H.: The Evaluation of Antihypertensive Procedures, with Particular Reference to their Effects on blood Pressure. Ann. Int. Med. **43:** 1161 (Dec.), 1955. Abstracted, Circulation **14:** 1113 (Dec.), 1956.

Hughes, W., and Warren, P. K. G.: Chronic Cerebral Hypertensive Disease. Geriatrics **4:** 8 (Jan.), 1956.

The authors describe a syndrome that they have named chronic cerebral hypertensive disease. Their description is based on a series of 72 middle-aged and elderly patients. The symptoms include emotional lability and intellectual deterioration. The signs include hypertensive (or a past history of this), evidence of hemiplegia, pseudobulbar palsy, and ophthalmic findings of narrowing and silver-wiring of the arteries and dilatation of the veins. On postmortem examination, multiple small infarcts were found bilaterally in the caudate nuclei and putamen.

RINZLER

PATHOLOGY

Glushien, A. S., and Fisher, E. R.: Renal Lesions of Sulfonamide Type after Treatment with Acetazolamide (Diamox). J. A. M. A. **160:** 204 (Jan.), 19 6.

Diamox is a widely used as a diuretic agent. The authors report a patient with Hodgkin's Disease who received Diamox for 4 days and who showed no clinical evidence of renal failure or sulfonamide intoxication. At autopsy 24 days later renal lesions indistinguishable from those produced by the antibacterial sulfonamides were present. This is the first report of renal lesion following the administration of Acetazolamide.

KITCHELL

Gross-Brockhoff, F., and Schreiber, H. W.: Pericardial Angiosarcoma. Ztschr. Kreislaufforsch. **44:** 867, 1955.

This is the fifth published case of pericardial angiosarcoma; this appeared in a 29-year-old woman and terminated in death after 1¼ years. The clinical pattern was that of pleural and pericardial effusion, but pericardial paracentesis disclosed only blood in the pericardial cavity while roentgenologically a double contour of the right atrium made the diagnosis of pericardial tumor likely. The electrocardiogram showed low voltage and depression of S-T in leads I and III.

LEPESCHKIN

Stresemann, E.: Endocardial Fibrosis in Infants. Arch. Kreislaufforsch. **23:** 77, 1955.

A histologic study of 4 cases showed proliferation of fibrous tissue not only in the endocardium but also in the subendocardial muscle layers and the conducting system; the vacuolization in these structures is attributed to impaired metabolism. One of the cases had a persistent ductus arteriosus, another coarctation of the aorta.

LEPESCHKIN

Dudley, H. R., Goodale, F., and O'Neal, R. M.: Fibro-Elastic Hamartomas of Heart Valves. Am. J. Path. **32:** 35 (Jan.–Feb.), 1956.

In a series of 50 autopsied cases, 19 hearts showed a total of 22 fibroelastic hamartomas. The majority are said to be in individuals dying in the seventh and eighth decades of life; however, the age distribution of cases is not given. The pathologic description, both gross and microscopic, is given with excellent illustrations. There was no clinical evidence of valvular dysfunction during life. The incidence of hamartomas in this series is significantly higher than in other reported series.

HARVEY

Bundley, P., and Stembridge, V. A.: Aneurysms of Aorta: A Clinico-Pathologic Study of 369 Necropsy Cases. Am. J. Path. **32:** 67 (Jan.–Feb.), 1956:

The authors present a summary of findings in regard to aortic aneurysm found at autopsy in a survey of 9,273 autopsies done at the University of Texas Medical Branch, Galveston, between the years 1892 and 1953. Four hundred and twelve aortic aneurysms were found in 369 cases. The majority were found in individuals in their fifth, sixth, and seventh decades. Sixty-one per cent occurred in Negroes. Eighty-three per cent occurred in males. Abdominal aneurysms occurred more commonly in the white male. Syphilis caused 54 per cent of these, arteriosclerosis 21 per cent, cystic medial necrosis 10 per cent, with congenital, mycotic, and unknown cause as the etiologic situation in the remainder. Saccular aneurysm was the most common type. Clinical features were well correlated with the location of the aneurysm. In abdominal and dissecting aneurysms 80 per cent of the individuals showed cardiac hypertrophy that was unexplained. The cause of death varied but rupture occurred in almost 40 per cent and heart failure in 25 per cent.

HARVEY

Busch, W.: New Measurements of the Thickness and Weight of the Ventricles in Various Forms of Hypertrophy, with Special Consideration of the Histologic Findings. Arch. Kreislaufforsch. **22:** 267, 1955.

The average normal weight of the free wall of the right ventricle was 50 Gm., that of the left ventricle and septum was 180 Gm. (the epicardial fat, the valves, and the great vessels were always removed and the heart treated with 10 per cent formaldehyde less than 30 minutes after death, before it went into rigor). In 8 cases of right ventricular hypertrophy the wall of this ventricle weighed 60–220 per cent more than normal while its average thickness was 3.7 mm. at the apex, 5.5 mm. at the base anteriorly and 9.5 mm. at the base posteriorly. In 9 cases of left ventricular hypertrophy the left wall and septum weighed up to 215 per cent more than normal and the average values for the thickness of the wall at the apex were 9.5 mm., at the base anteriorly 17.4 mm. and posteriorly 14.4 mm. Measurements of the left ventricle in rigor showed greater thickness than that shown by the ventricle hypertrophied to 3 times the normal thickness. which was not in rigor. The concept of "concentric left ventricular hypertrophy" probably originated through measurements in rigor and is an artifact. In cases with primary right ventricular hypertrophy there was usually also some left ventricular hypertrophy, but in those with primary left hypertrophy there was no definite relationship to right hypertrophy. In right ventricular hypertrophy there was always a corresponding hypertrophy of myocardial fibers usually without degenerative changes; in severe left hypertrophy theer were usually degenerative changes in addition to hypertrophy (sometimes spotty) of myocardial fibers, and usually also marked fatty infiltration of the right ventricle. In 13 cases without hypertrophy the average thickness of the ventricles at the apex, anterior basal wall and posterior basal wall were 1.9, 3.2, 5.0 and 7.5, 12.0, 11.7 mm. respectively. In 1 case of myocardial infarction vicarious hypertrophy of muscle fibers was found in the normal parts of the left ventricle.

LEPESCHKIN

PATHOLOGIC PHYSIOLOGY

Lawrence, G. H., Zimmerman, H. B., Bercu, B. A., and Burford, T. H.: Evaluation of Mitral and Aortic Valvular Disease by Left Heart Catheterization. Surg., Gynec. and Obst. **101:** 558 (Nov.), 1955. Abstracted, Circulation **14:** 853 (Nov.), 1956.

Nahas, G. G., and L'Allemand, H.: Circulation in Dogs after Respiratory Arrest Induced by Curare. J. Appl. Physiol. **8:** 468 (Jan.), 1956.

Survival of animals during pentothal-induced apnea has been attributed to diffusion oxygenation of blood or diffusion respiration. Resuscitation from diffusion respiration under the combination of pentothal and intocostin was more uncertain than when pentothal alone was used, although the physiologic variables studied were the same. The present study was accomplished in order to investigate pulmonary blood flow after cessation of respiration produced by d-tubocurarine under light pentothal anesthesia, in order to eliminate as much as possible the depressive effect of barbiturates on the circulation.

Mongrel dogs were studied by means of cardiac output by the dye-dilution method, electrocardiograms, mean arterial blood pressures, pulmonary artery and vein pressures, alveolar gas samples, and blood pH. These measurements were made during a control period, a 15-minute period of respiratory arrest induced by 0.1 mg. per Kg. of body weight of d-tubocurarine and then alternate periods of controlled breathing, during which time the animal was denitrogenated and breathing by apneic oxygenation. During the first period of respiratory arrest the tracheal valve was open to 100 per cent O_2, (apneic oxygenation), but it was opened to air during the second period of respiratory arrest (apneic hypoxia).

Apneic oxygenation and apneic hypoxia caused a fall in heart rate and a rise in the mean arterial blood pressures in the pulmonary artery and the pulmonary vein. There were no significant changes in the electrocardiogram. During apneic oxygenation, arterial blood was fully saturated with oxygen while CO_2 content of the blood rose from 37 to 56 vols. per cent, pH fell to 7.10, pCO_2 of alveolar air rose to 146 mm. Hg. During apneic hypoxia, arterial O_2 saturation varied from 25 to 75 per cent. Cardiac output rose toward the end of the 15-minute period of respiratory arrest. Calculated pulmonary vascular resistance fell during apneic oxygenation but not during apneic hypoxia. There was no change in calculated peripheral vascular resistance.

The increase in mean arterial blood pressure may be attributed to CO_2 retention which stimulates adrenaline production. This hypertension is not caused by peripheral vasoconstriction, which does not occur, and is probably related to the increase in cardiac output. The observed bradycardia is probably caused by the known increased sensitivity of the heart to vagal stimulation during respiratory acidosis, later by the rise in CO_2 and hypertension by means of the carotid sinus reflex. Other studies of respiratory arrest utilized pentothal sodium. The results indicated that the barbiturate may have depressed the myocardium and, therefore, eliminated the increase in cardiac output found here. Furthermore, the vagal inhibitory effects of pentothal may have prevented the bradycardia found here.

Respiratory arrest was induced in dogs by d-tubocurarine. Circulatory studies during 15-minute periods of "apneic oxygenation" and "apneic hypoxia" revealed an increase in pressures in the systemic arteries and pulmonary vessels, as well as a marked bradycardia. Possible mechanisms for these changes were discussed.

WECHSLER

Klepzig, H., Kindermann, G., and Reindell, H.: Concerning the Question of Sensitivity of the Heart to Hypoxia in Athletes. Ztschr. Kreislaufforsch. **45:** 8 (Jan.), 1956.

Inhalation of 10 per cent oxygen for 10 minutes led to the same degree of T wave lowering in the limb leads in 23 average normal persons and 45 outstanding athletes but to a greater degree in 20 patients with circulatory disturbances. S-T depression or inversion of T in I–II appeared only in patients with pathologic hypertrophy of the left ventricle (19 cases). Athletes with large hearts showed smaller T wave changes than those with small hearts. These changes are usually more pronounced after 5 minutes than after 10 minutes of hypoxia and are interpreted as resulting from changes in vegetative nerve tonus rather than from myocardial hypoxia. Previous results of others according to which the large hearts of athletes are more susceptible to hypoxic changes in the electrocardiogram are interpreted as resulting from lack of quantitation of hypoxia and from the fact that few outstanding athletes were studied.

LEPESCHKIN

Paquet, E.: The Diagnostic Approach to Auricular Myxomas. Canad. M. A. J. **74:** 121 (Jan.), 1956.

The diagnosis of atrial myxoma is made by the following findings: mitral stenosis without rheumatic history; symptomatic variability with postural changes; progressively severe heart failure not improved by the usual treatment; confirmatory findings at angiocardiography and cardiac catheterization. These tumors are pedunculated and benign, so that surgical removal is indicated. Patients operated on so far have not survived because of technical or organic difficulties.

BERNSTEIN

Gerard, R., and Benyamine, R.: Pulmonary Capillary Pressures in Mitral Disease. An Attempt at Schematization. Arch. mal. coeur **49:** 31 (Jan.), 1956.

Pulmonary wedge pressure curves in 81 cases with mitral valve disease were analyzed and compared with other hemodynamic and clinical findings. According to the morphology of the wedge curve and the presence or absence of atrial fibrillation, the material could be divided into several groups with different clinical aspects. In the presence of sinus rhythm, pure mitral stenosis reveals M-shaped wedge pressure curves of 3 different types. In the first type, the first peak is smaller than the second, the capillary pressure is low, the pulmonary arterial pressure is normal, and the mitral lesion clinically insignificant. In the second group, where the 2 peaks are about equal in size, the wedge pressure is elevated upon exercise and pulmonary arterial pressure is somewhat increased, indicating a moderate degree of mitral block. In the third group, which is characterized by a larger second peak of the wedge pressure curve, both wedge and pulmonary arterial pressures are high but the gradient between the 2 is large. In these cases, increased pulmonary arterial resistance is present in addition to the mitral block. The wedge pressure curves obtained in this third group resemble those in mitral regurgitation. However, the 2 conditions can be distinguished by the fact that in mitral insufficiency, in contrast to mitral stenosis, the second peak has a "tent-shaped" appearance, the maximal value of the wedge pressure approaches the systolic pressure in the pulmonary artery and the ratio of maximal and end-diastolic wedge pressure values equals or is more than 2.

The distinction of these 3 clinical types of mitral stenosis by different contours of the wedge pressure curves is not possible in the presence of atrial fibrillation. In this condition the appearance of the wedge pressure curve is inconstant and largely dependent on the variability of the duration of the ventricular cycle and the diastolic filling time.

PICK

Shaffer, A. B., and Silber, E. N.: Factors Influencing the Character of the Pulmonary Arterial Wedge Pressure. Am. Heart J. **51:** 522 (Apr.), 1956.

Appraisal of the contour of pulmonary wedge pressure curves of 63 human subjects with normal hemodynamics, rheumatic valvular disease, or congenital heart disease, in relation to pulmonary arteriolar resistance, mean pulmonary wedge pressure and, in one third of the cases, left atrial pulse contour, led to the following conclusions concerning the transmission of the left atrial pressure pulse to the wedged catheter: 1. When both pulmonary arteriolar resistance and mean pulmonary wedge pressure are low, it is hypothesized that transmission mainly via the pulmonary capillaries leads to damped pulmonary wedge pressure curves, while transmission via pulmonary arteriovenous anastomoses results in undamped pulmonary wedge pressure curves. 2. When the left atrial-pulmonary capillary system is distended, as reflected by an elevated mean pulmonary wedge pressure or mean left atrial pressure, transmission is undamped, apparently independently of arteriovenous anastomoses. 3. When pulmonary arteriolar resistance is greatly elevated, transmission is mainly damped, regardless of the level of pulmonary wedge pressure. In all cases where both wedge pressure curves and left atrial curves were obtained, mean pulmonary wedge pressure corresponded closely to mean left atrial pressure. The incidence of confirmatory blood samples in cases of normal hemodynamics and in the various disease states corresponds roughly with the fidelity with which wedge pressure pulse contour reflects left atrial pressure pulse contour.

RINZLER

SURGERY AND CARDIOVASCULAR DISEASES

Julian, O. C., Grove, W. J., Dye, W. S., Sadove, M. S., Javid, H., and Rose, R. F.: Hypotension and Hypothermia in Surgery of the Thoracic Aorta. Arch. Surg. **70:** 729 (May), 1955.

The combined use of hypotension (Arfonad-induced) and hypothermia (cooling perfusion blanket or ice packs) is reported in 19 patients undergoing surgery of the thoracic aorta.

Two patients underwent resection of the upper descending aorta for aneurysms immediately below the subclavian artery. In each case the preparation for high aortic occlusion was body cooling to 82 F. Occlusion times were 30 and 68 min. No ischemic damages resulted in abdominal viscera or spinal cord. One patient died on the twelfth postoperative day of hemorrhage from rupture of the aorta distal to the resection.

Nine adult patients were cooled, 6 to a significant degree, in preparation for resection of coarctation. In all these patients the defect was closed with a preserved homologous graft. In each of the 11 patients the blood pressure was reduced to a marked extent before the occluding clamp was applied.

No untoward effects were noted from the combined use of hypotension and hypothermia.

MAXWELL

Warden, H. E., DeWall, R. A., Read, R. C., Aust, J. B., Cohen, M., Varco, R. L. and Lillehei, C. W.: Total Cardiac By-Pass Utilizing Continuous Perfusion from Reservoir of Oxygenated Blood. Proc. Soc. Exper. Biol. & Med. **90:** 246 (Oct.), 1955.

A simple method permitting total bypass of the heart and lungs for the performance of intracardiac surgical operations is described. This method utilizes continuous perfusion of the recipient's (patient's) arterial system from a reservoir of oxygenated blood. An equivalent quantity of venous blood is removed

from the recipient's superior and inferior cavae. A pump is utilized to control this exchange between the recipient and the arterial and venous reservoirs. Arterial blood for the reservoir was obtained from a donor animal used as an oxygenator independent of the perfusion system. This was done by collecting arterial blood from the donor's femoral artery into a heparin-glucose solution while stored venous blood was infused into his femoral vein at an equal rate. Ordinarily 2,000 to 3,500 ml. of arterial blood were collected from a single donor dog in this fashion. The optimum dose of heparin to prevent clotting in the arterial blood collected was 25 to 32 mg./L. of blood. The simplifications of the clinical application of this method are briefly discussed.

MAXWELL

Bruce, R. A., and Merendino, K. A.: Effects of Potassium and Cortisone on Morbidity and Hyponatremia Following Mitral Valve Surgery. Am. J. M. Sc. **230:** 392 (Oct.), 1955.

Patients undergoing mitral valvulotomy have occasionally manifested an unexpected morbidity during the first postoperative week. Evidence of an increased total body sodium and water with hyponatremia, renal conservation of sodium and water, and a decreased exchangeable potassium has been presented. The effects of potassium and cortisone upon the morbidity and metabolic responses of 12 patients subjected to such surgery are described in this report. The administration of potassium was associated with the appearance of mild hyperkalemia in 3 patients given the chloride salt. Of the 9 patients given cortisone, 1 exhibited mental symptoms; none developed either hyponatremia or hyperkalemia when fluid and sodium intake were limited. Cortisone was regarded as a useful adjunct in the treatment of circulatory collapse with pressor amines in 1 patient. It was concluded that fluids and sodium administration should be limited in the postoperative management of patients undergoing mitral valve surgery. Potassium should be given only as fruit juices or beef broth as tolerated by the patient rather than as supplemental potassium salts. Cortisone may be of value in occasional patients experiencing profound stress. It did not prevent pericarditis in 5 of 9 patients treated with this agent.

SHUMAN

Krosnick, A., and Wasserman, F.: Cardiac Arrhythmia in the Older Age Group Following Thoracic Surgery. Am. J. M. Sc. **230:** 541 (Nov.), 1955.

Ten cases are reported of cardiac arrhythmia in 82 patients of 50 years or older following thoracic surgery. The operative procedures included thoracotomy for purposes of exploration, biopsy or resection, exclusive of procedures on the heart. The arrhythmias observed were paroxysmal atrial fibrillation in 7 instances, paroxysmal atrial flutter in 2 instances, and ventricular tachycardia in 1 instance. In only 1 case did the arrhythmia develop after the first postoperative week. Seven of the patients had clinical evidence of heart disease prior to surgery. The operative procedures performed on these patients included left pneumonectomy in 4, right pneumonectomy in 3, lobectomy in 1, and subtotal esophagectomy in 2. The arrhythmias resulted in 2 deaths. Predisposing factors in the irregular heart action include age, pre-existing heart disease, antecedent arrhythmias, extent of surgery, electrolyte imbalance, drugs, and anemia. Anoxia, vagal reflexes, and hypotension are considered the major precipitating factors. Treatment of arrhythmias includes prophylaxis with correction of anemia, electrolyte imbalance, prevention of anoxia and hypotension, and active treatment with digitalis and antifibrillatory drugs such as procaine amide or quinidine.

SHUMAN

Bliss, E. L., Rumel, W. R., and Hardin Branch, C. H.: Psychiatric Complications of Mitral Surgery. Arch. Neurol. & Psychiat. **74:** 249 (Sept.), 1955.

The appearance of 2 schizophrenic reactions after mitral surgery prompted the authors to determine the frequency of major psychiatric complications in those who had undergone mitral surgery. Other groups have reported emotional disturbances following this type of surgery.

The records of 37 patients who underwent mitral surgery were analyzed for psychiatric data. This type of data was sparse because of the emphasis on difficult medical and surgical problems. Two patients developed schizophrenic reactions after surgery. One had been psychotic previously and the operation caused a recandescence of his schizophrenic process. Two other patients experienced short-lived schizophrenic reactions after surgery, 1 having delusions and the other auditory hallucinations. One patient had a clearly defined reaction characteristic of an organic confusional state. One other patient had a similar episode, but it was not described in enough detail. Six patients were sufficiently anxious and depressed to merit comments by both physicians and nurses. Two case histories of postoperative schizophrenia are described in detail. One individual died of electro-shock therapy.

These results suggest the possibility that mitral surgery may be a greater psychologic threat than other major surgical procedures and chronic rheumatic patients may be particularly vulnerable under these circumstances. The usefulness and risk of electroshock therapy in the treatment of these schizophrenic reactions have been indicated.

WECHSLER

Linton, R. R., and Menendez, C. V.: Arterial Homografts: A Comparison of the Results with End-to-End and End-to-Side Anastomoses. Ann. Surg. **142:** 568 (Oct.), 1955.

The authors point out that in the end-to-end anastomosis of grafts for the treatment of segmental arterial thrombosis 60 per cent failures occur. Because of such results they attempted to study the efficacy of end-to-side anastomosis. With the latter procedure none of the grafts became occluded and the only failures were in 2 patients secondary to sepsis. It was pointed out that a longer period of follow-up on such cases was necessary to obtain a true evaluation of the method.

ABRAMSON

Ciocatto, E., and Cattaneo, A. D.: Experimental and Clinical Results with Controlled Hypothermia. Anesthesiology **17:** 17 (Jan.), 1956.

Experimental studies of controlled refrigeration in animals showed that the survival of low temperatures was improved when low body temperatures were reached quickly and when ganglionic-blocking agents were administered prior to refrigeration. With the technic of refrigeration plus ganglionic-blocking agents, cardiac disturbance such as ventricular fibrillation, otherwise so frequently noted with hypothermia alone, was almost absent and the mortality rate of the procedure was maintained within reasonable limits.

The current management in the employment of controlled hypothermia as part of the surgical treatment in human beings is presented. The measures consist of the intramuscular administration of an antihistamine (usually Fargan) 2 hours prior to surgery, the intravenous administration of a ganglionic blocker (usually Pendiomide) 1 hour before surgery, and the starting of refrigeration about 15 min. later. A rectal temperature of about 27 C. is reached usually in about 45 min. and then refrigeration is stopped. If shivers develop, Pentothal is given, otherwise only oxygen is administered during the subsequent phases of the procedure. Rewarming is begun as soon as the main surgical steps are completed. During surgery adequate blood replacement is carefully watched. The postoperative period is treated as usual.

Clinical experience with 91 patients subjected to controlled hypothermia indicates that this method is of value in surgical procedures where the blood supply to the vital organs must be interrupted for a period of time for the performance of the corrective measures and also in other conditions in which hypoxia is severe. The procedure is well tolerated in both children and adults for long periods of time and the mortality is low. This method markedly reduces the frequency and severity of accidents commonly associated with cardiac surgery. The safety of the method is increased by refrigerating and rewarming as quickly as possible and utilizating ganglion inhibiting drugs.

SAGALL

Horton, R. E.: Use of Grafts in Treatment of Atherosclerosis of Lower Limbs. Brit. M. J. **1:** 81 (Jan. 14), 1956.

In a series of 29 patients with atherosclerotic obstruction of the arteries of the lower limb, grafting was performed. In distinction to the experience with grafting in more proximal arteries, a high incidence of thrombosis, both early and delayed, led the author to conclude that grafting by the end-to-end technic is not worthwhile beyond the proximal part of the femoral artery. End-to-side grafts may prove more successful.

MCKUSICK

Cooley, D. A., Mahaffey, D. E., and DeBakey, M. E.: Total Excision of the Aortic Arch for Aneurysm. Surg., Gynec. & Obst. **101:** 667 (Dec.), 1955.

The authors report a case in which total arch resection was accomplished under hypothermia by temporary bypass shunts. The latter, made of compressed polyvinyl sponge, conducted blood from the ascending to the descending aorta and also into the innominate and left common carotid arteries. The patient died on the sixth day postoperatively. Autopsy revealed that the prosthesis was intact and contained no thrombi.

ABRAMSON

THROMBOEMBOLIC PHENOMENON

Krahl, E., Pratt, G. H., Doehner, G., and Rousselot, L. M.: The Intra-Aortic Administration of Fibrinolytic Enzymes in Peripheral Emboli Experimentally Induced in the Aorta. Am. J. Surg. **90:** 965 (Dec.), 1955.

The authors produced experimental emboli in the aorta of dogs with clotted blood, and then a polyethylene catheter was introduced into the vessel above the clot. A solution of highly purified crystalline line trypsin was injected into the aorta through the catheter. Arteriograms were used to determine the location of the emboli and the effect of the trypsin on them.

It was found that trypsin did not have a rapid lytic effect upon hard organized thrombi in dogs. In fact, in dilute doses this substance appeared to initiate a clot.

ABRAMSON

Lenégre, J., Gerbaux, A., Scebat, L., and Leconte des Floris, R.: Four New Observations of Chronic Cor Pulmonale Caused by Pulmonary Arterial Thrombosis: A Clinical and Hemodynamic Study. Arch. mal. coeur **48:** 1132 (Dec.), 1955.

The authors describe diagnostic features of a particular type of chronic cor pulmonale caused by pulmonary arterial thrombosis secondary to pulmonary embolism. The diagnosis is suggested when an embolic episode is sooner or later followed by chronic right heart failure. Angiocardiography reveals filling

defects in the pulmonary circulation with exclusion of major or minor segments of the lung fields. At cardiac catheterization the pulmonary arterial pressure is elevated, while the wedge pressure is normal. Cardiac output, however, in contrast to the ordinary type of chronic cor pulmonale, is reduced. In the over-all clinical and hemodynamic picture, chronic cor pulmonale due to pulmonary arterial thrombosis resembles that of "primary" pulmonary hypertension. The necessity to distinguish the 2 conditions is pointed out in view of the possibility of treating thrombotic cor pulmonale by anticoagulants or surgical intervention.

PICK

Wright, I. S., and Foley, W. T.: Pulmonary Embolism and Infarction: Diagnosis and Management. Am. J. Surg. **90:** 440 (Sept.), 1955.

The authors discuss the diagnosis and treatment of pulmonary embolism and infarction. They point out that these conditions are frequently overlooked and misdiagnosed in clinical practice, particularly pulmonary emboli which by themselves do not produce detectable x-ray abnormalities. Only if there is a profound change in lung tissue, progressing to necrosis (pulmonary infarction), will radiologic alterations be produced.

Pain is often the first and most prominent symptom. This may be due to the reaction of the pleura overlying the infarction or it may follow severe anoxia of tissue. Dyspnea commonly accompanies the pain, as well as cough associated with hemoptysis.

Frequent findings are fever, tachycardia and signs of consolidation of lung tissue. The x-ray generally demonstrates a shadow, the shape, size, and density depending on the angle which the infarct makes to the direction of the x-rays. Electrocardiographic changes depend in great part upon the increase in pulmonary artery pressure, which is reflected in dilatation of the right ventricle, producing "right heart strain."

Among the complications of massive pulmonary infarction are cor pulmonale, characterized by readily recognized clinical signs and shock.

Treatment primarily involves prevention of the condition. According to the authors, ligation of the main veins of the lower extremities and even of the inferior vena cava are not prophylactic measures of choice. They prefer properly administered anticoagulant therapy, especially after a thrombosis or a pulmonary embolus has been recognized.

ABRAMSON

VASCULAR DISEASE

Dembowski, U., Hasse, H. M., and Köble, H.: Complications During Angiography. Ztschr. Kreislaufforsch. **44:** 959, 1955. Abstracted, Circulation **14:** 1083 (Dec.), 1956.

Hoye, S. J., and Warren, R.: Follow-up Studies of Iliofemoral Arterial Reconstruction in Arteriosclerosis Obliterans. New England J. Med. **254:** 102 (Jan. 19), 1956. Abstracted, Circulation **14:** 1128 (Dec.), 1956.

Blake, T. M.: Arteriosclerosis: The Present Status of the Problem. South. M. J. **48:** 1080 (Oct.), 1955.

The author reviews several aspects of the problem of arteriosclerosis. He points out that little has been added to the knowledge of the morphology of the disease. However, 1 point worthy of emphasis is the frequency with which hemorrhage occurs within atheromata. Most of the available evidence supports filtration from the blood stream with subsequent phagocytosis by macrophages as the mechanism responsible for the entrance of lipids into the vessel wall.

Very wide variations in the amount of cholesterol ingested have no influence on its concentration in the blood. As a result, the enthusiasm for its restriction as a means of controlling the formation of atheromatous plaques, has waned. Another point of interest in this regard is the accepted fact that cholesterol is synthesized endogenously.

The author emphasizes that the preoccupation with the serum cholesterol is based on the hypothesis of simple causal relationship between hypercholesterolemia and atherosclerosis. However, such a view does not take into account the fact that neutral fats and phospholipids are also constituents of atheromata.

ABRAMSON

Keating, D. R.: Thrombosis of Pulmonary Arteries. Am. J. Surg. **90:** 447 (Sept.), 1955.

The author describes the clinical picture of thrombosis of the pulmonary artery and presents 4 cases of this type. He points out that organized thrombi can occlude large branches of the pulmonary artery for long periods of time and yet produce little disability in proportion to the critical function of the vessels involved. This is probably the result of slow progression in the size of the thrombi, the occurrence of recanalization, and limitation in the number of large pulmonary arterial branches involved.

Onset of massive pulmonary artery thrombosis is most commonly observed in pulmonary embolism arising from systemic veins or the right ventricle. It may also occasionally be a complication of local pathologic processes, such as carcinoma of the lung, pulmonary tuberculosis, and congenital and acquired heart disease.

Most often the symptoms of chronic massive thrombosis of pulmonary arteries are those of right heart failure. Dyspnea is a universal complaint. Death in all cases is sudden and unexpected.

The clinical diagnosis of the condition is in large measure dependent upon the radiographic examination of the chest. The pertinent finding is enlarge-

ment of one or more of the vessels in the hilar regions or enlargement of the pulmonary artery itself. On fluoroscopy the thrombosed artery possesses little motion and, as a result, produces sharp, clear images on the x-ray film. It has an elliptic configuration, tapering abruptly at the distal point of thrombotic closure. Distal to the site of thrombosis the lung segment involved exhibits reduced radiability due to diminished blood flow in the affected pulmonary segments.

The electrocardiogram generally reveals signs of right ventricular hypertrophy; angiocardiograms are also of aid in diagnosis.

ABRAMSON

Ricketts, H. T.: The Problem of Degenerative Vascular Disease in Diabetes. Am. J. Med. **19:** 933 (Dec.), 1955.

Diabetes, or some related factor, hastens the onset, and increases the frequency and severity of arterial and arteriolar sclerosis. It gives rise to capillary lesions of the renal glomeruli and retina that belong almost exclusively to the diabetic state. Diabetes increases susceptibility to atherosclerosis to a greater extent in women than in men, and the former have a greater incidence of intercapillary glomerulosclerosis but not of retinopathy. Duration of diabetes is the most important single factor in the development of vascular disease, and its effects are greater in younger persons than in older persons. The highest frequency of advanced lesions occurs in severely diabetic patients with prolonged, heavy glycosuria. However, some patients with mild, well-controlled diabetes have manifest vascular lesions while their opposite numbers seem to escape. These inconsistencies support the yet unproved concept that hereditary tendencies may be as important as diabetes itself.

The experimental production of both glomerular and retinal lesions with cortisone and corticotrophin strengthens the possibility that they have a common pathogenesis in man and raises the question of whether their clinical occurrence is related to adrenal hyperactivity. Mucopolysaccharides are increased in the blood of diabetic patients with vascular, especially renal, disease but to some extent in those without it, and may be related to the pathogenesis of retinopathy and intercapillary glomerulosclerosis.

Hyperlipemia in the treated diabetic patient is neither so frequent nor so marked as has been commonly supposed. Its association with atherosclerosis is loose and inconstant and in many cases is lacking entirely. Elevated lipid levels in intercapillary glomerulosclerosis are probably a result rather than a cause of the disease. The etiology and pathogenesis of diabetic vascular disease remains obscure.

HARRIS

Sapp, O. L., Arney, G. K., and Mattingly, T. W.: Determination of Arterial Blood Pressure in the Lower Extremity. J.A.M.A. **159:** 1727 (Dec. 31), 1955.

Determination of the arterial blood pressure in the lower extremity is of particular value in the diagnosis of conditions such as congenital coarctation of the aorta, acquired occlusive diseases of the aorta and large arteries of the lower extremities, extrinsic compression of the aorta, and aortic aneurysms. It is pointed out that the presence of palpable pulses in the peripheral arteries of the lower extremity does not necessarily exclude these conditions. In the studies made of arterial blood pressure values obtained in the thigh with a nonstandard 18 cm. sphygmomanometer cuff and the standard 12-cm. arms cuff shows a significant difference, especially in the level of the systolic pressure. The values obtained with the 18 cm. cuff more closely approximate the intra-arterial reading in the femoral artery than do the values obtained from the use of the 12 cm. or the 15.5 cm. cuff in the normal adult patient. This and the ease of application makes the larger cuff the more desirable diagnostic tool. However, it is important that the examining physician recognize the difference and when different-sized cuffs are used they should be so defined in order that values be properly determined and evaluated. It is thought that the committee on standardization of blood pressure of the American Heart Association should give consideration to a standard for procedure and normal values for blood pressure readings in the lower extremity.

KITCHELL

Lenegre, J., Gerbaux, A., Scebat, L., and Leconte des Floris, R.: Four New Observations of Chronic Cor Pulmonale due to Arterial Pulmonary Thrombosis. Arch. mal. coeur **48:** 1132 (Dec.), 1955.

In all 4 cases, chronic right ventricular failure appeared without apparent cause or subsequent to thromboembolic disease. Angiography showed extensive defects in the pulmonary arterial tree; the pulmonary arterial pressures were very high (63–109 mm. Hg) while the pulmonary capillary pressures were normal. Contrary to cases of chronic cor pulmonale due to bronchial disease, these cases also showed a decreased cardiac output. All cases showed a marked "P pulmonale" pattern, marked right axis deviation, high R or R′ in V_1 and depressed S-T with diphasic or negative T in V_1 up to V_5–V_6. Contrary to cases of chronic cor pulmonale of respiratory origin, deep S waves in V_1–V_6 did not appear. These 4 cases are very similar to many published cases of apparently "idiopathic" pulmonary hypertension.

LEPESCHKIN

Mathieu, L., Hadot, S., Pernot, C., and Metz: Two Cases of Obliterating Arteritis of the Supra-Aortic Trunks in Young Women (Takayasu's Disease). Arch. mal. coeur **48:** 1172 (Dec.), 1955.

In this syndrome the arterial pulse in the arms

disappears completely, and weakness without trophic disturbances appears in the hands. In 1 case orthostatic syncope was present. One case had aortic insufficiency.

LEPESCHKIN

Nichols, C. W., Jr., Lindsay, S., and Chaikoff, I. L.: Production of Arteriosclerosis in Birds by the Prolonged Feeding of Dihydrocholesterol. Proc. Soc. Exper. Biol. & Med. **89:** 609 (Aug.–Sept.), 1955.

Twelve chickens were fed a diet containing 0.5 per cent dihydrocholesterol (DHC) for 6 months. Twelve controls were used. It was shown that the feeding of DHC for long periods of time induced extensive arteriosclerosis of the thoracic and abdominal aortas. The aortic and hepatic lesions in the DHC-fed birds were identical with those resulting from the feeding of cholesterol. Crystals found in the aortic lesions appeared larger than cholesterol crystals and gave a negative test for cholesterol. These were presumed to be dihydrocholesterol crystals. Hepatic enlargement in DHC-fed birds was similar to that observed in cholesterol-fed birds, and was due, in part, to reticuloendothelial storage of dihydrocholesterol.

MAXWELL

Finlayson, R., and Robinson, J. O.: Giant-Cell Arteritis of the Legs. Brit. M. J. **2:** 1595 (Dec. 31), 1955.

The authors describe a 75-year-old woman who appears to have had giant-cell arteritis localized to arteries of the legs and producing gangrene. Both legs were amputated. Although it is now established that temporal arteritis is a generalized disorder that may involve the central retinal artery, cerebral arteries, and the aorta and its larger branches, affection of the vessels of the extremities has been described only rarely.

MCKUSICK

Harrison, R. J., Harrison, C. V., and Kopelman, H.: Giant-Cell Arteritis with Aneurysms. Effects of Hormone Therapy. Brit. M. D. **2:** 1593 (Dec. 31), 1955.

Giant-cell arteritis as a cause of aneurysms of large vessels, including the aorta, even with dissection and rupture, has been described in occasional cases. The authors point out that 2 factors, intraluminal pressure and size of the lumen, determine the stress on the wall. Since giant-cell arteritis incites marked intimal thickening, this factor may prevent the production of aneurysms in small vessels.

A 56-year-old housewife had lassitude, weight loss, and night sweats followed by a painless swelling in the right side of the neck and right infraclavicular region. Aneurysms of the right external carotid and the subclavian arteries were discovered. There was early clubbing of the fingers of the right hand. In this and a second patient with more conventional temporal arteritis cortisone and ACTH were therapeutically effective.

MCKUSICK

Sibthorpe, E. M.: Antenatal Pulmonary Embolism. A Report of Three Cases. Brit. M. J. **2:** 1063, (Oct. 29), 1955.

The author reports these cases because seemingly, in contradistinction to the puerperium, pulmonary embolism is rare in the antenatal period. When it does occur, however, it is probably an unusually grave complication. One maternal death and 2 fetal deaths occurred in this group of 3 patients. The author urges that antenatal thrombophlebitis be treated in hospitals.

MCKUSICK

Horvath, S. M., Albaugh, E., and Hamilton, L.: Demonstration of Collateral Circulation During Acute Obstructions of the Thoracic Aorta. Am. J. Physiol. **183:** 193 (Nov.), 1955.

In these experiments the thoracic aorta was occluded at the level of the fourth interspace. During the period of occlusion a collateral circulation was demonstrated between the thoracic and abdominal aorta. The connection seemed to be mainly by means of the anterior spinalis arteries. The anastomosis is effective within a few seconds after the thoracic aorta is obstructed.

OPPENHEIMER

Alvarez, W. C.: More about Little Strokes. Geriatrics **10:** 555 (Dec.), 1955.

A little stroke is characterized by transient aphasia, numbness somewhere in the body, or weakness in 1 arm or leg. Often momentary dizziness, confusion, or nausea may occur. Sudden changes in character, temperament and ability should arouse suspicion of a little stroke. These strokes may repeat themselves over a period of years. Less usual symptoms are given, such as burning in the skin, pain in the abdomen, and pain in the shoulder and abdomen. Case histories are given as illustrations.

RINZLER.

Ellis, F. H., Jr., Helden, R. A., and Hines, E. A., Jr.: Aneurysm of the Abdominal Aorta Involving the Right Renal Artery: Report of Case with Preservation of Renal Function after Resection and Grafting. Ann. Surg. **142:** 992 (Dec.), 1955.

The authors described a case of an abdominal aortic aneurysm involving the right renal artery which was treated surgically. The inferior mesenteric artery was ligated at its origin and the aneurysm was resected. Continuity was restored by anastomosing the upper end of the thoracic aortic homograft to the proximal cut end of the patient's abdominal aorta. The distal end of the graft was anastomosed to the patient's common iliac artery, while the left common

iliac artery was anastomosed to the left lateral side of the graft. The stump of the celiac axis of the graft was anastomosed to the cut end of the patient's right renal artery. The postoperative course was uncomplicated. An excretory urogram taken before discharge from the hospital showed prompt excretion of dye through both kidneys.

It is of interest that the right renal artery was occluded for 135 min. during aortic resection and replacement by a homograft and that, despite this, satisfactory renal function was observed.

ABRAMSON

Garritano, R. P., Wohl, G. T., Kirby, C. K., and Pietroluongo, A. L.: The Roentgenographic Demonstration of an Arteriovenous Fistula of Renal Vessels. Am. J. Roentgenol. **75:** 905 (May), 1956.

The authors present a case report of a renal arteriovenous aneurysm, presumably on a traumatic (gun shot) basis. This was suspected because of a continuous murmur in the abdominal left upper quadrant and contiguous region posteriorly, plus increased pulse pressure and left ventricular enlargement. Confirmation was obtained by means of a translumbar aortography. Nephrectomy was performed when conditions did not permit local repair.

SCHWEDEL

Toes, N. A.: Ruptured Splenic Arterial Aneurysm during Parturition. Brit. M. J. **1:** 495 (Mar. 3), 1956.

Sheehan and Falkiner in 1948 pointed out that of the 417 reported female cases of splenic arterial aneurysm below the age of 40 years, 23 were pregnant, and rupture nearly always occurred at 7 to 9 months' gestation.

The author describes a 22-year-old primigravida who went into circulatory collapse and died a few hours after delivery. Mild hypertensive toxemia had been present in the last weeks of gestation. Furthermore, the second stage of delivery was more than usually burdensome to the patient.

MCKUSICK

Edholm, P., and Seldinger, S. I.: Percutaneous Catheterization of the Renal Artery. Acta radiol. **45:** 15 (Jan.), 1956.

The authors describe in detail the method of selectively visualizing 1 or the other renal artery with radiopaque dye. Through a Seldinger percutaneous arterial needle a polythene catheter tip (shaped by heat then cooling) is passed under fluoroscopic control into the desired artery. The opacifying substance is then injected under controlled pressure.

The authors indicate that aberrant renal branches occur in as often as 22 per cent of reported cases, and that these are not filled by the selective method. Such areas of nonopacification might erroneously be interpreted as filling defects due to tumor or infarct, thus lessening the value of this procedure.

SCHWEDEL

Odman, P.: Percutaneous Selective Angiocardiography of the Main Branches of the Aorta. Acta radiol. **45:** 1 (Jan.), 1956.

The author describes a method of selectively passing a radiopaque polythene catheter into the aorta, thence to the artery under consideration. Formerly the entire region was suffused with the opacifying fluid, at times resulting in undesirable effects. Since ordinary polythene catheters become soft and pliable at body temperatures the author immerses the catheter in hot water, cools it rapidly, shaping the terminal portion so that it might more readily be guided under fluoroscopic control into a main arterial branch. The catheter is introduced percutaneously through an arterial needle. Side orifices near the tip serve to reduce recoil and displacements during the period of injecting the opacifying substance at high pressures.

Twenty selective angiograms have been performed by this method. Excellent illustrations are offered of filling of subclavian arteries in scalenus anticus syndrome, postoperative axillary aneurysm, Blalock procedure for tetralogy of Fallot, and celiac and renal artery visualizations.

SCHWEDEL

OTHER SUBJECTS

Zoll, P. M., Linenthal, A. J., Norman, L. R., Paul, M. H., and Gibson, W.: External Electric Stimulation of the Heart in Cardiac Arrest. Arch. Int. Med. **96:** 639 (Nov.), 1955. Abstracted, Circulation **14:** 187 (Aug.), 1956.

Eckstein, R. W.: Development of Interarterial Coronary Anastomoses by Chronic Anemia: Disappearance Following Correction of Anemia. Circulation Research **3:** 306 (May), 1955. Abstracted, Circulation **14:** 343 (Sept.), 1956.

Holman, D. V.: Venesection, before Harvey and after. Bull. New York Acad. Med. **31:** 661 (Sept.), 1955. Abstracted, Circulation **14:** 567 (Oct.), 1956.

Clark, E. G., and Danbolt, N.: The Oslo Study of the Natural History of Untreated Syphilis. J. Chron. Dis. **2:** 311 (Sept.), 1955. Abstracted, Circulation **14:** 592 (Oct.), 1956.

McKusick, V. A.: Carcinoid Cardiovascular Disease. Bull. Johns Hopkins Hosp. **98:** 13 (Jan.), 1956. Abstracted, Circulation **14:** 1068 (Dec.), 1956.

AMERICAN HEART ASSOCIATION, INC.

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Telephone Gramercy 7-9170

THE 1957 HEART FUND

The 1957 Heart Fund campaign, which is expected to surpass the mark of $17,755,000 set by the 1956 campaign, will be conducted during the month of February. The most concentrated drive for funds will occur on Heart Sunday, February 24, when the volunteers representing 56 affiliates and more than 350 chapters of the American Heart Association will call on millions of citizens to contribute to the Heart Fund.

Admiral Richard E. Byrd is Chairman of the 1957 Heart Fund campaign. Serving with him as Co-Chairman is Kenneth C. Royall, former U. S. Secretary of War.

Last year's Heart Fund totals exceeded the previous year's fund drive by $4,180,000. The national office will allocate more than 50 per cent of its campaign income—or about two million dollars—for the support of research in the form of fellowships or grants-in-aid. In addition, a substantial portion of the funds retained by local Heart Associations is utilized for the support of scientific investigations. Since 1948, when the Association became a national voluntary health agency, close to $20,000,000 has been expended for research support by national, state and local Heart Associations. It is confidently expected that this year more money than ever before will become available to finance the Association's programs in research, community service programs, public and professional education.

In one of the Assembly Panels at last year's Annual Meeting in Cincinnati, physicians participating in a discussion on fund raising and public relations stressed the fact that doctors not only should, but do play a key role in the Heart Fund drive. Their participation has been valuable in the recruitment of community leadership, in speeches acquainting the general public with the facts of research and cardiovascular disease and in explaining patient needs. In many instances, local rehabilitation and research programs could best be interpreted to the general public by physicians who participated in press conferences and interviews or radio and TV appearances.

LIST OF AHA FELLOWSHIPS AND RESEARCH GRANTS AVAILABLE

A booklet containing a complete list of AHA fellowships and research grant awards for the year 1956–57 is available from the Medical Division, American Heart Association. The 52-page brochure lists the Association's 3 Career Investigators, the continued and new Established Investigators as well as Research Fellows. A listing of continued and new grant awards completes the booklet. Included in the information are the names of the fellowship recipients and their institutions; length of fellowships; a brief description of each project; and, in the case of grants-in-aid, the sum awarded. The various categories of awards and principles and procedures governing their allocation are discussed in a foreword.

WORK AND THE HEART TO BE SUBJECT OF WISCONSIN CONFERENCE IN MAY

The First Wisconsin Conference on Work and the Heart will take place at Marquette University School of Medicine in Milwaukee, May 15–18.

Sponsored jointly by the Wisconsin Heart Association, the American Heart Association, the National Heart Institute and the Industrial Health Council of the American Medical Association, the conference will present a review, analysis and discussion of all available data related to the effect of work on the heart. The various meetings will permit an assessment of fundamental techniques currently employed by specialists in rehabilitation and work evaluation projects. Attendance will be by invitation only.

There will be panels in physiology, pathology, work evaluation and workmen's com-

pensation. In each of the panels, 10 or 12 speakers will present a 10-minute summary of a formal paper followed by a 20-minute discussion period. Dr. Paul D. White will serve as chairman of the final session and comment on the summaries of the individual panels. Many leading specialists from the U.S. and from abroad are expected to participate in the conference.

Besides Dr. Paul D. White, Dr. Leonard J. Goldwater, Professor of Occupational Medicine, Columbia University, Dr. E. A. Irvin, Chairman, Rehabilitation Committee, American Heart Association, Dr. Richard J. Clark, Boston, member of the Committee, and Dr. Frederick A. Whitehouse, Director of Rehabilitation, American Heart Association, will attend the conference.

CARDIOVASCULAR RESEARCH TRAINING PROGRAM

A new one-year term of the unique postgraduate cardiovascular research and training program at the Medical College of Georgia in Augusta will start on July 1. It will permit about 5 postdoctoral students to receive an intensive training in cardiovascular research under the direct supervision of Dr. William F. Hamilton, President of the American Physiological Society and Professor of Physiology, and Dr. Raymond P. Ahlquist, Professor of Pharmacology.

The program includes classical experiments, use of modern instruments in physiology, pharmacology and surgery, utilization of delicate meters to measure the blood flow and, later on, the carrying out of individual research projects by students either working jointly or with faculty members. It is sponsored by the American Heart Association and the National Heart Institute of the U. S. Public Health Service.

The course is conducted at the Departments of Physiology and Pharmacology, Medical College of Georgia in Augusta. A stipend of $3,400 plus $350 for each dependent and certain expenses will be provided to participants who will be given time to read classical and current research reports.

Inquiries and requests for application forms should be addressed to either of the directors of the program, Dr. W. F. Hamilton or Dr. R. P. Ahlquist at the Medical College of Georgia.

AMERICAN SOCIETY FOR THE STUDY ARTERIOSCLEROSIS ELECTS NEW OFFICERS

The American Society for the study of Arteriosclerosis has elected as its new President Charles F. Wilkinson, M.D., Professor and head, Department of Medicine, Postgraduate Medical School, New York University, New York City. Reelected as Secretary and Treasurer was Dr. O. J. Pollak, pathologist, Kent General Hospital, Dover, Del.

LONDON WILL CELEBRATE HARVEY TERCENTENARY IN JUNE

The Tercentenary of the death of William Harvey, (1578–1657), British discoverer of the circulation of the blood, will be commemorated by an International Congress on Circulation next June. The Congress' main theme will be a "review of the present knowledge of circulation." It will be held at the Royal College of Surgeons, 11, Chandos Street, Cavendish Square, London, W. 1, England, June 3–June 7.

The program features many prominent cardiologists from England, Switzerland, Germany, Sweden, France, Canada and the United States. Among the latter are Lasker Award winner Dr. Louis N. Katz, Chicago, and Nobel Prize winner Dr. Andre Cournand, New York.

Topics to be discussed include the following: knowledge of the circulation from the seventeenth to the twentieth century; the role of the heart in circulation; the results of cardiac surgery; the coronary and pulmonary circulation, the foetal and the cerebral circulation.

The Congress will be followed by a week-end conference on the more personal and biographical aspects of William Harvey's life at his birthplace in Folkestone, Kent.

NATIONAL HEALTH FORUM WILL MEET IN CINCINNATI, MARCH 20–22

The theme of the 1957 National Health Forum will be "Better Mental Health—Challenge to all Health Services," according to Dr. Francis J. Braceland, Chairman of the program

committee for the Forum. The Forum, an annual series conducted by the National Health Council in behalf of its 51 national organization members, will meet in Cincinnati's Hotel Netherland-Hilton, March 20–22. Dr. Braceland, who is Psychiatrist-in-Chief at the Institute of Living, Hartford, Connecticut, and President of the American Psychiatric Association, will be one of the Forum's keynote speakers. Other keynote speakers who will address the meeting on March 20 are Dr. Harold D. Lasswell, Professor of Law and Political Science, Yale University, and Jack R. Ewalt, Director of the Joint Commission on Mental Illness and Health. The Forum will seek to outline what is now known about mental health and how more effective use of that knowledge can be encouraged.

SEND SUBSCRIPTION RENEWAL ORDERS TO GRUNE AND STRATTON, INC.

Renewal orders for the official journals of the American Heart Association, *Circulation* and *Circulation Research*, should be sent directly to the publisher, Grune and Stratton, Inc., 381 Fourth Ave., New York 16, N. Y., who has been authorized by the Association to handle all subscriptions to these journals, whether from members of the Association, or from nonmembers.

THIRD WORLD CONGRESS TO BE HELD IN BRUSSELS IN 1958

The date for the Third World Congress of Cardiology to be held in Brussels, Belgium, has been set at September 14–21, 1958.

Five volumes containing outstanding papers and panels of the Second World Congress of Cardiology held in Washington in September, 1954, have been published by Paul D. Hoeber, Inc., Medical Book Department, Harpers & Bros. through an arrangement with the American Heart Association. The volumes, obtainable directly from the publisher (49 East 33rd Street, New York 16, N. Y.), bear the title "World Trends in Cardiology."

MEETINGS CALENDAR

January 14: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.

January 15: Conference on Atherosclerosis and Coronary Heart Disease, New York. Miss Helen O'Shaughnessey, New York Heart Association, 485 Fifth Avenue, N. Y.

January 16–18: Conference on Cerebral Vascular Diseases, Princeton, N. J. Irving S. Wright, M.D., Cornell Medical Center, 1300 York Ave., New York 21. (By invitation.)

January 16–19: Neurosurgical Society of America, Palm Springs, California. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N. Y.

January 25: American Federation for Clinical Research, (Southern Section), New Orleans. Samuel P. Martin, M.D., J. Hillis Miller Health Center, University of Florida College of Medicine, Gainesville, Fla.

January 30–31: American Federation for Clinical Research, (Western Section), Carmel, California. Sherman M. Mellinkoff, M.D., Department of Medicine, School of Medicine, University of California Medical Center, Los Angeles 24, Calif.

February 4–6: American Academy of Allergy, Los Angeles. Francis C. Lowell, 65 E. Newton St., Boston, Mass.

February 8–9: American College of Radiology, Chicago. W. G. Stronach, 20 N. Wacker Dr. Chicago 6, Ill.

February 11: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.

February 14: Symposium on Present Status of Heart Sound Production and Recording, University of Buffalo, Buffalo, N. Y.

March 4–6: National Biophysics Conference, Columbus, Ohio. Samuel A. Talbot, Department of Medicine, Johns Hopkins Hospital, Baltimore 5, Md.

March 11: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.

March 19: National Advisory Committee of Local Health Departments, Cincinnati. Miss Martha Luginbuhl, National Advisory Committee, 1790 Broadway, New York, N. Y.

March 20–22: Annual Meeting of the National Health Council, Cincinnati. National Health Forum Registration, National Health Council, 1790 Broadway, New York 19, N. Y.

March 25–28: American Academy of General Practice, St. Louis. Mr. Mac F. Cahal, Volker Blvd., Kansas City 12, Mo.

April 8–12: American College of Physicians, Boston. Mr. E. R. Loveland, 4200 Pine St., Philadelphia, Pa.

April 11–13: American Association of Pathologists and Bacteriologists, Washington, D. C. Edward A. Gall, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 15–19: American Society for Experimental Pathology, Chicago. Cyrus C. Erickson, 858 Madison Ave., Memphis 3, Tenn.

April 22–27: American Academy of Neurology, Boston. T. W. Framer, University of North Carolina, Chapel Hill, N. C.

April 28–May 2: Society for American Bacteriologists, Detroit. J. W. Bailey, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

May 4–5: American Psychosomatic Society, Atlantic City. Morton F. Reiser, 451 Madison Ave., New York 22, N. Y.

May 5: American Federation for Clinical Research, Atlantic City, N. J. William W. Stead, Veterans Hospital, Minneapolis 17, Minn.

May 5–10: National Tuberculosis Association, Kansas City, Mo. Mrs. Morrell DeReign, 1790 Broadway, New York 19, N. Y.

May 6–9: American Urological Association, Pittsburgh. Samuel L. Raines, 188 S. Bellevue Blvd., Memphis, Tenn.

May 7–8: Association of American Physicians, Atlantic City, N. J. P. B. Beeson, Yale University School of Medicine, New Haven, Conn.

May 8–10: American Surgical Association, Chicago. R. Kennedy Gilchrist, 59 E. Madison St., Chicago, Ill.

May 13: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.

May 15–18: First Wisconsin Conference on Work and the Heart, Milwaukee. Elston L. Belknap, M.D., Marquette University School of Medicine, 561 N. 15th St., Milwaukee 3, Wis. (By Invitation.)

June 2: American Society for Vascular Surgery, New York. Henry Swan, 4200 East 9th Ave., Denver 20, Colo.

ABROAD

February 24–28: Biennial International Scientific Congress, International College of Surgeons, Mexico City. Dr. Max Thorek, International College of Surgeons, 850 Irving Park Rd., Chicago 13, Ill.

June 3–7: Harvey Tercentenary Congress, London. D. Geraint James, M.D., M.R.C.P. 11 Chandos Street, Cavendish Square, London W.1., England.

June 23–28: International Congress on Rheumatic Diseases, Toronto, Ont. International Congress on Rheumatic Diseases, P. O. Box 237, Terminal "A", Toronto, Ontario, Canada.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

American Heart Association

Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections*

By Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis,
Charles H. Rammelkamp, Chairman

This article is the second revision of the American Heart Association statement on the prevention of rheumatic fever issued January 1953. This statement was prepared by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis appointed by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. The committee is cognizant of the fact that no recommendations of any group can be final at this time. The present approach may not be the eventual solution of the problem of preventing rheumatic fever. Revisions and changes will be made as new knowledge may indicate.

RHEUMATIC fever is a recurrent disease which in most instances can be prevented. Since both the initial and recurrent attacks of the disease are precipitated by infections with group A streptococci, prevention of rheumatic fever and rheumatic heart disease depends upon the control of streptococcal infections. This may be accomplished by (1) early and adequate treatment of streptococcal infections in *all* individuals and (2) prevention of streptococcal infections in *rheumatic* subjects.

Treatment of Streptococcal Infections in the General Population

Following epidemics and in certain population groups, it has been found that about 3 per cent of untreated streptococcal infections are followed by rheumatic fever. Adequate and early penicillin treatment, however, will eliminate streptococci from the throat and prevent most attacks of rheumatic fever.

Diagnosis of Streptococcal Infection

In some instances streptococcal infections can be recognized by their clinical manifestations. *In many patients, however, it is impossible to determine the streptococcal nature of a respiratory infection without obtaining throat cultures.* The following section on diagnosis has been included in order to assist physicians in making a positive diagnosis and assuring adequate treatment.

The accurate recognition of individual streptococcal infections, their adequate treatment and the control of epidemics in the community presently offer the best means of preventing initial attacks of rheumatic fever.

Common Symptoms

Sore throat—sudden onset, pain on swallowing.

Headache—common.

Fever—variable, but generally from 101 to 104F.

Abdominal pain—common, especially in children; less common in adults.

Nausea and vomiting—common, especially in children.

Common Signs

Red throat.

Exudate—usually present.

Glands—swollen, *tender* lymph nodes at angle of jaw.

Rash—scarlatiniform.

Acute otitis media, Acute sinusitis } frequently due to the streptococcus.

In the absence of the common symptoms and signs, occurrence of any of the following symptoms is usually not associated with a

* Copies of this report can be obtained from the American Heart Association and its affiliates.

streptococcal infection: simple coryza; hoarseness; cough.

Laboratory Findings

*Throat Culture**—hemolytic streptococci are almost invariably recovered on culture during acute streptococcal infections.

White Blood Count—generally over 12,000.

Treatment of Streptococcal Infections

When streptococcal infection is suspected, treatment should be started immediately. Penicillin is the drug of choice. Effective blood levels should be maintained for a *period of 10 days* to prevent rheumatic fever by eradicating the streptococci from the throat.

Penicillin may be administered by either intramuscular or oral route. Intramuscular administration is recommended as the method of choice since it ensures adequate blood levels for a sufficient length of time. Oral therapy by contrast is dependent upon the cooperation of the patient.

In the treatment of streptococcal infections *in known rheumatic* subjects, parenteral penicillin should be employed in at least the maximum doses recommended below.

Recommended Treatment Schedules

Intramuscular Penicillin

Benzathine Penicillin G. Children: One intramuscular injection of 600,000 to 900,000 U. Adults: One intramuscular injection of 900,000 to 1,200,000 U.

Procaine Penicillin with Aluminum Monostearate in Oil. Children: One intramuscular injection of 300,000 U. every third day for three doses. Adults: One intramuscular injection of 600,000 U. every third day for three doses.

Oral Antibiotics

To prevent rheumatic fever by eradicating streptococci, therapy must be continued *for the entire 10 days* even though the temperature returns to normal and the patient is asymptomatic.

Penicillin. Children and adults: 200,000 to 250,000 U. three times a day *for a full 10 days.*

Other Antibiotics. Broad spectrum antibiotics such as erythromycin and the tetracyclines are useful in patients who are sensitive to penicillin. If given *for 10 days,* these antibiotics are probably as effective as *oral* penicillin in the treatment of streptococcal infections but are subject to the same uncertainties of administration by the oral route.

Not Recommended

The following therapy is *not effective* in preventing rheumatic fever when used as treatment for streptococcal infections: sulfonamide drugs; penicillin troches or lozenges.

Prevention of Streptococcal Infections in Rheumatic Individuals

Many streptococcal infections occur without producing clinical manifestations. For this reason, prevention of recurrent rheumatic fever must depend on continuous prophylaxis rather than solely on treatment of acute attacks of streptococcal disease.

Recommendations for Prophylaxis

Who should be treated? In general, all patients who have a *well-documented history* of rheumatic fever or chorea, or who show *definite evidence* of rheumatic heart disease, should be given continuous prophylaxis.

Although recurrent attacks of rheumatic fever occur at any age, the risk of recurrences decreases with the passage of years. Some physicians may wish to make exceptions to instituting prophylaxis in certain of their adult patients, particularly those without heart disease who have had no rheumatic attacks for many years.

How long should prophylaxis be continued?

* An outline of a recommended "Method for Culturing Beta Hemolytic Streptococci from the Throat" may be obtained from the office of the American Heart Association. This outline is based on the chapter on streptococci by Armine T. Wilson, M.D., for the fourth edition of *Diagnostic Procedures and Reagents,* to be published by the American Public Health Association. With the permission of the American Public Health Association, full reprints of this chapter will become available on request from the office of the American Heart Association upon publication of the fourth edition of this reference work (1957).

The risk of acquiring a streptococcal infection and the possibility of rheumatic fever recurrences continue throughout life. It is, therefore, suggested that the safest general procedure is to continue prophylaxis indefinitely.

When should prophylactic treatment be initiated?

ACTIVE RHEUMATIC FEVER: As soon as the diagnosis of rheumatic fever is made or any time thereafter when the patient is first seen. The streptococcus should be eradicated with penicillin (see schedules) following which the prophylactic regimen is instituted.

INACTIVE RHEUMATIC FEVER: In inactive rheumatic fever, prophylaxis should be instituted when the patient is first seen.

Should prophylaxis be continued during the summer? Yes, continuously. Streptococcal infections can occur at any season although they are more prevalent in the winter.

Prophylactic Methods—Intramuscular and Oral

Oral medication depends on patient cooperation. In most instances failures of sulfonamide or penicillin prophylaxis occur in patients who fail to ingest the drug regularly. This can be avoided by long-acting depot penicillin given intramuscularly once a month.

Benzathine Penicillin G—Intramuscular

Dosage: 1,200,000 U. once a month.

Toxic reactions: Same types as with oral penicillin but occur more frequently and tend to be more severe. Some local discomfort usually is experienced.

Sulfadiazine—Oral

This drug has the advantage of being easy to administer, inexpensive and effective. (Other newer sulfonamides are probably as effective.) Although resistant streptococci have appeared during mass prophylaxis in the armed forces, this is rare in civilian populations.

Dosage: From 0.5 to 1.0 Gm. once a day. The smaller dose is to be used in children under 60 pounds.

Toxic Reactions: Infrequent and usually minor. In any patient being given sulfonamides, consider all rashes and sore throats as possible toxic reactions especially if they occur in the first 8 weeks. In patients on this prophylactic regimen it is hazardous to treat toxic reactions or intercurrent infections with sulfonamides.

Chief Toxic Reactions:

Skin Eruptions. Morbilliform, continue drug with caution. Urticaria or scarlatiniform rash associated with sore throat or fever: discontinue drug.

Leukopenia. Discontinue if white blood count falls below 4,000 and polynuclear neutrophiles below 35 per cent because of possible agranulocytosis which is often associated with sore throat and a rash. Because of these reactions, weekly white blood counts are advisable for the first 2 months of prophylaxis. The occurrence of agranulocytosis after 8 weeks of continuous prophylaxis with sulfonamides is extremely rare.

Penicillin—Oral

Penicillin has the desirable characteristics of being bactericidal for group A streptococci and of rarely producing serious toxic reactions. A careful history of allergic reactions and previous response to penicillin should be obtained.

Dosage: 200,000 to 250,000 U. once or twice a day. The latter is probably more effective.

Toxic reactions: Urticaria and angioneurotic edema. Reactions similar to serum sickness include fever and joint pains and may be mistaken for rheumatic fever.

Although many individuals who have had reactions to penicillin may subsequently be able to tolerate the drug, it is safer not to use penicillin if the reaction has been severe and particularly if angioneurotic edema has occurred.

Protection of Rheumatic Fever Patients in Hospital Wards

Patients with rheumatic fever or rheumatic heart disease are often exposed to increased hazards in hospital wards as the result of contact with streptococcal carriers or patients with active streptococcal infections. Protection of the rheumatic patient is imperative because of the high rate or recurrence of rheumatic fever following streptococcal infection. In addition

to the customary precautions employed to prevent cross infections, the following procedures are recommended:

All hospital patients with streptococcal infections should be fully treated by one of the methods outlined in order to eliminate streptococci and avoid the carrier state.

Patients admitted with acute rheumatic fever should immediately receive a full course of antibiotic therapy, whether or not streptococci are isolated from the throat. As soon as the therapeutic course is completed, continuous streptococcal prophylaxis should be instituted.

Patients with inactive rheumatic fever or rheumatic heart disease should be placed on continuous streptococcal prophylaxis on admission to the hospital or as soon thereafter as the diagnosis is established.

Prophylaxis Against Bacterial Endocarditis

In individuals who have rheumatic or congenital heart disease, bacteria may lodge on the heart valves or other parts of the endocardium, producing bacterial endocarditis. Transient bacteremia which may lead to bacterial endocarditis is known to occur following various surgical procedures including dental extractions and other dental manipulations which disturb the gums, the removal of tonsils and adenoids, giving birth, and operations on the gastrointestinal or urinary tracts. It is good medical and dental practice to protect patients with rheumatic or congenital heart disease by prophylactic measures.

Recommended Prophylactic Methods

Penicillin is the drug of choice for administration to patients with rheumatic or congenital heart disease undergoing dental manipulations, or surgical procedures in the oral cavity.

Although the exact dosage and duration of therapy are somewhat empirical, there is some evidence that for effective prophylaxis reasonably high concentrations of penicillin must be present at the time of the dental procedure. The dosage regimens employed for long-term prophylaxis of rheumatic fever are inadequate for this purpose. High levels of penicillin in the blood over a period of several days are recommended to prevent organisms from lodging in the heart valves during the period of transient bacteremia.

Not only should penicillin prophylaxis be designed to afford maximum protection, but the method must also be practical. In general, the combined oral and parenteral route of administration is preferred. All patients should be instructed to report to their physician or clinic should they develop a fever within a month following the operation.

First Choice—Intramuscular and Oral Penicillin Combined

For 2 days prior to surgery—200,000 to 250,000 U. by mouth 4 times a day. On day of surgery—200,000 to 250,000 U. by mouth 4 times a day *and* 600,000 U. aqueous penicillin with 600,000 U. procaine penicillin shortly before surgery. For 2 days after—200,000 to 250,000 U. by mouth 4 times a day.

Second Choice—Oral Penicillin

200,000 to 250,000 units 4 times a day beginning 2 days prior to the surgical procedure and continued through the day of surgery or dental procedure and 2 days thereafter.

Contraindications

A history of sensitivity to penicillin.

Other Antibiotics

Erythromycin or the broad spectrum antibiotics should be employed as prophylaxis in patients who are sensitive to penicillin. In those who are undergoing surgery of the urinary or lower gastrointestinal tract, oxytetracycline or chlortetracycline should be administered in full dosage for 5 days, beginning treatment 2 days prior to the surgical procedure.

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